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(54) Title: BENZOTHIOPHENE HYDROXAMIC ACID DERIVATIVES WITH CARBAMATE, UREA, AMIDE AND SULFONAMIDE SUBSTITUTIONS

(57) Abstract: The present invention relates to a novel class of hydroxamic acid derivatives carbamate, urea, amide and sulfonamide substitutions. The hydroxamic acid compounds can be used to treat cancer. The hydroxamic acid compounds can also inhibit histone deacetylase and are suitable for use in selectively inducing terminal differentiation, and arresting cell growth and/or apoptosis of neoplastic cells, thereby inhibiting proliferation of such cells. Thus, the compounds of the present invention are useful in treating a patient having a tumor characterized by proliferation of neoplastic cells. The compounds of the invention are also useful in the prevention and treatment of TRX-mediated diseases, such as autoimmune, allergic and inflammatory diseases, and in the prevention and/or treatment of diseases of the central nervous system (CNS), such as neurodegenerative diseases. The present invention further provides pharmaceutical compositions comprising the hydroxamic acid derivatives and safe dosing regimens of these pharmaceutical compositions, which are easy to follow, and which result in a therapeutically effective amount of the hydroxamic acid derivatives *in vivo*.



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TITLE OF THE INVENTION

BENZOTHIOPHENE HYDROXAMIC ACID DERIVATIVES WITH CARBAMATE, UREA, AMIDE
AND SULFONAMIDE SUBSTITUTIONS

5 FIELD OF THE INVENTION

The present invention relates to a novel class of hydroxamic acid derivatives with carbamate, urea, amide and sulfonamide substitutions. The hydroxamic acid compounds can be used to treat cancer. The hydroxamic acid compounds can also inhibit histone deacetylase and are suitable for use in selectively inducing terminal differentiation, and arresting cell growth and/or apoptosis of neoplastic
10 cells, thereby inhibiting proliferation of such cells. Thus, the compounds of the present invention are useful in treating a patient having a tumor characterized by proliferation of neoplastic cells. The compounds of the invention are also useful in the prevention and treatment of TRX-mediated diseases, such as autoimmune, allergic and inflammatory diseases, and in the prevention and/or treatment of diseases of the central nervous system (CNS), such as neurodegenerative diseases.

15

BACKGROUND OF THE INVENTION

Compounds having a hydroxamic acid moiety have been shown to possess useful biological activities. For example, many peptidyl compounds possessing a hydroxamic acid moiety are known to inhibit matrix metalloproteinases (MMPs), which are a family of zinc endopeptidases. The MMPs play a
20 key role in both physiological and pathological tissue degradation. Therefore, peptidyl compounds that have the ability to inhibit the action of MMPs show utility for the treatment or prophylaxis of conditions involving tissue breakdown and inflammation. Further, compounds having a hydroxamic acid moiety have been shown to inhibit histone deacetylases (HDACs), based at least in part on the zinc binding property of the hydroxamic acid group.

25 The inhibition of HDACs can repress gene expression, including expression of genes related to tumor suppression. Inhibition of histone deacetylase can lead to the histone deacetylase-mediated transcriptional repression of tumor suppressor genes. For example, inhibition of histone deacetylase can provide a method for treating cancer, hematological disorders, such as hematopoiesis, and genetic related metabolic disorders. More specifically, transcriptional regulation is a major event in cell differentiation,
30 proliferation, and apoptosis. There are several lines of evidence that histone acetylation and deacetylation are mechanisms by which transcriptional regulation in a cell is achieved (Grunstein, M., *Nature*, 389: 349-52 (1997)). These effects are thought to occur through changes in the structure of chromatin by altering the affinity of histone proteins for coiled DNA in the nucleosome. There are five types of histones that have been identified. Histones H2A, H2B, H3 and H4 are found in the nucleosome, and H1
35 is a linker located between nucleosomes. Each nucleosome contains two of each histone type within its core, except for H1, which is present singly in the outer portion of the nucleosome structure. It is believed

that when the histone proteins are hypoacetylated, there is a greater affinity of the histone to the DNA phosphate backbone. This affinity causes DNA to be tightly bound to the histone and renders the DNA inaccessible to transcriptional regulatory elements and machinery.

The regulation of acetylated states occurs through the balance of activity between two enzyme complexes, histone acetyl transferase (HAT) and histone deacetylase (HDAC).

The hypoacetylated state is thought to inhibit transcription of associated DNA. This hypoacetylated state is catalyzed by large multiprotein complexes that include HDAC enzymes. In particular, HDACs have been shown to catalyze the removal of acetyl groups from the chromatin core histones.

It has been shown in several instances that the disruption of HAT or HDAC activity is implicated in the development of a malignant phenotype. For instance, in acute promyelocytic leukemia, the oncoprotein produced by the fusion of PML and RAR alpha appears to suppress specific gene transcription through the recruitment of HDACs (Lin, R.J. *et al.*, *Nature* 391:811-14 (1998)). In this manner, the neoplastic cell is unable to complete differentiation and leads to excess proliferation of the leukemic cell line.

U.S. Patent Numbers 5,369,108, 5,932,616, 5,700,811, 6,087,367 and 6,511,990, the contents of which are hereby incorporated by reference, disclose hydroxamic acid derivatives useful for selectively inducing terminal differentiation, cell growth arrest or apoptosis of neoplastic cells. In addition to their biological activity as antitumor agents, these hydroxamic acid derivatives have recently been identified as useful for treating or preventing a wide variety of thioredoxin (TRX)-mediated diseases and conditions, such as inflammatory diseases, allergic diseases, autoimmune diseases, diseases associated with oxidative stress or diseases characterized by cellular hyperproliferation (U.S. Application No. 10/369,094, filed February 15, 2003, the entire content of which is hereby incorporated by reference). Further, these hydroxamic acid derivatives have been identified as useful for treating diseases of the central nervous system (CNS) such as neurodegenerative diseases and for treating brain cancer (See, U.S. Application No. 10/273,401, filed October 16, 2002, the entire content of which is hereby incorporated by reference).

The inhibition of HDAC by the hydroxamic acid containing compound suberoylanilide hydroxamic acid (SAHA) disclosed in the above referenced U.S. Patents, is thought to occur through direct interaction with the catalytic site of the enzyme as demonstrated by X-ray crystallography studies (Finnin, M.S. *et al.*, *Nature* 401:188-193 (1999)). The result of HDAC inhibition is not believed to have a generalized effect on the genome, but rather, only affects a small subset of the genome (Van Lint, C. *et al.*, *Gene Expression* 5:245-53 (1996)). Evidence provided by DNA microarrays using malignant cell lines cultured with a HDAC inhibitor shows that there are a finite (1-2%) number of genes whose products are altered. For example, cells treated in culture with HDAC inhibitors show a consistent induction of the cyclin-dependent kinase inhibitor p21 (Archer, S. Shufen, M. Shei, A., Hodin, R. *PNAS* 95:6791-96 (1998)). This protein plays an important role in cell cycle arrest. HDAC inhibitors are thought to increase the rate of transcription of p21 by propagating the hyperacetylated state of histones in the

region of the p21 gene, thereby making the gene accessible to transcriptional machinery. Genes whose expression is not affected by HDAC inhibitors do not display changes in the acetylation of regional associated histones (Dressel, U. *et al.*, *Anticancer Research* 20(2A):1017-22 (2000)).

Further, hydroxamic acid derivatives such as SAHA have the ability to induce tumor cell growth arrest, differentiation and/or apoptosis (Richon *et al.*, *Proc. Natl. Acad. Sci. USA*, 93:5705-5708 (1996)). These compounds are targeted towards mechanisms inherent to the ability of a neoplastic cell to become malignant, as they do not appear to have toxicity in doses effective for inhibition of tumor growth in animals (Cohen, L.A. *et al.*, *Anticancer Research* 19:4999-5006 (1999)).

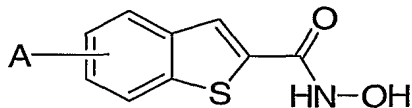
In view of the wide variety of applications for compounds containing hydroxamic acid moieties, the development of new hydroxamic acid derivatives having improved properties, for example, increased potency or increased bioavailability is highly desirable.

SUMMARY OF THE INVENTION

The present invention relates to a novel class of hydroxamic acid derivatives carbamate, urea, amide and sulfonamide substitutions. The hydroxamic acid compounds can be used to treat cancer. The hydroxamic acid compounds can also inhibit histone deacetylase and are suitable for use in selectively inducing terminal differentiation, and arresting cell growth and/or apoptosis of neoplastic cells, thereby inhibiting proliferation of such cells. Thus, the compounds of the present invention are useful in treating a patient having a tumor characterized by proliferation of neoplastic cells. The compounds of the invention are also useful in the prevention and treatment of TRX-mediated diseases, such as autoimmune, allergic and inflammatory diseases, and in the prevention and/or treatment of diseases of the central nervous system (CNS), such as neurodegenerative diseases. The present invention further provides pharmaceutical compositions comprising the hydroxamic acid derivatives, and safe, dosing regimens of these pharmaceutical compositions, which are easy to follow, and which result in a therapeutically effective amount of the hydroxamic acid derivatives *in vivo*.

It has been unexpectedly discovered that certain hydroxamic acid derivatives show improved activity as histone deacetylase (HDAC) inhibitors.

The present invention thus relates to compounds represented by Formula I and pharmaceutically acceptable salts, solvates and hydrates thereof, as detailed herein.



I

The foregoing and other objects, features and advantages of the invention will be apparent from the following more particular description of preferred embodiments of the invention.

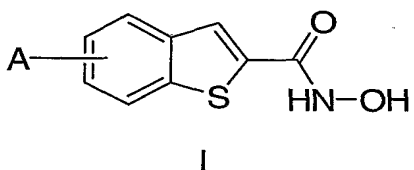
DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a novel class of hydroxamic acid derivatives having a benzothiophene or thiophene backbone. In one embodiment, the hydroxamic acid derivatives can inhibit histone deacetylase and are suitable for use in selectively inducing terminal differentiation, and arresting cell growth and/or apoptosis of neoplastic cells, thereby inhibiting proliferation of such cells. Thus, the compounds of the present invention are useful in treating cancer in a subject. The compounds of the invention are also useful in the prevention and treatment of TRX-mediated diseases, such as autoimmune, allergic and inflammatory diseases, and in the prevention and/or treatment of diseases of the central nervous system (CNS), such as neurodegenerative diseases.

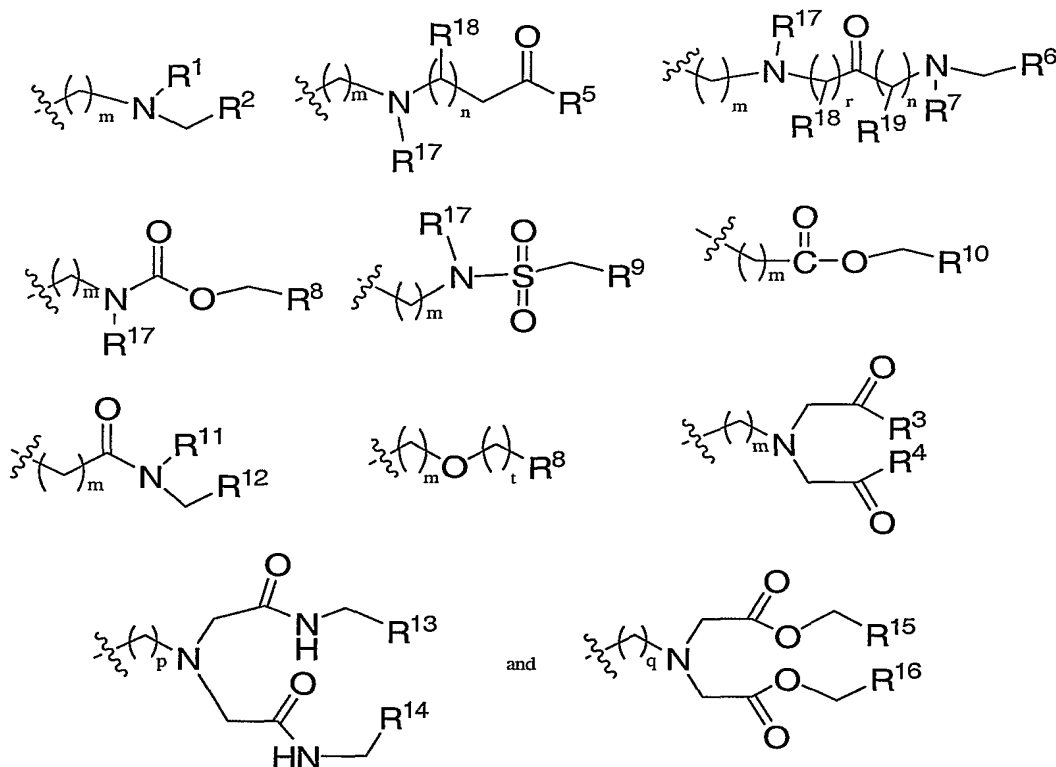
It has been unexpectedly and surprisingly discovered that certain hydroxamic acid derivatives, show improved activity as histone deacetylase (HDAC) inhibitors.

COMPOUNDS

The present invention relates to compounds represented by Formula I, i.e., hydroxamic acid derivatives, and/or stereoisomers (including enantiomers), racemates, pharmaceutically acceptable salts, solvates, hydrates or polymorphs thereof:



wherein A is a group selected from:



wherein R^2 to R^6 , R^8 to R^{10} and R^{12} to R^{16} are, independently of each other, a group selected from: substituted C_1 - C_{10} alkyl, substituted C_1 - C_{10} alkylaryl, substituted C_1 - C_{10} alkylcycloalkyl or substituted C_1 - C_{10} alkylheterocyclyl; wherein the alkyl portion of the group is substituted with a substituent that is independently selected from $-NR^{20}C(=O)R^{21}$, $-NR^{20}C(=O)OR^{21}$, $-C(=O)NR^{21}R^{22}$, $-NR^{20}SO_2R^{21}$ or $-NR^{20}C(=O)NR^{21}R^{22}$;

R^1 , R^7 , R^{11} and R^{17} to R^{20} are independently selected from hydrogen, unsubstituted or substituted C_1 - C_{10} alkyl, unsubstituted or substituted aryl, unsubstituted or substituted C_3 - C_8 cycloalkyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted C_1 - C_{10} alkylaryl, unsubstituted or substituted C_1 - C_{10} alkylcycloalkyl, or unsubstituted or substituted C_1 - C_{10} alkylheterocyclyl;

R^{21} is selected from unsubstituted or substituted C_1 - C_{10} alkyl, unsubstituted or substituted aryl, unsubstituted or substituted C_3 - C_8 cycloalkyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted C_1 - C_{10} alkylaryl, unsubstituted or substituted C_1 - C_{10} alkylcycloalkyl, or unsubstituted or substituted C_1 - C_{10} alkylheterocyclyl;

R^{22} is selected from hydrogen, unsubstituted or substituted C_1 - C_{10} alkyl, unsubstituted or substituted aryl, unsubstituted or substituted C_3 - C_8 cycloalkyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted C_1 - C_{10} alkylaryl, unsubstituted or substituted C_1 - C_{10} alkylcycloalkyl, or unsubstituted or substituted C_1 - C_{10} alkylheterocyclyl;

m , p and q are independently of each other 0, 1 or 2;

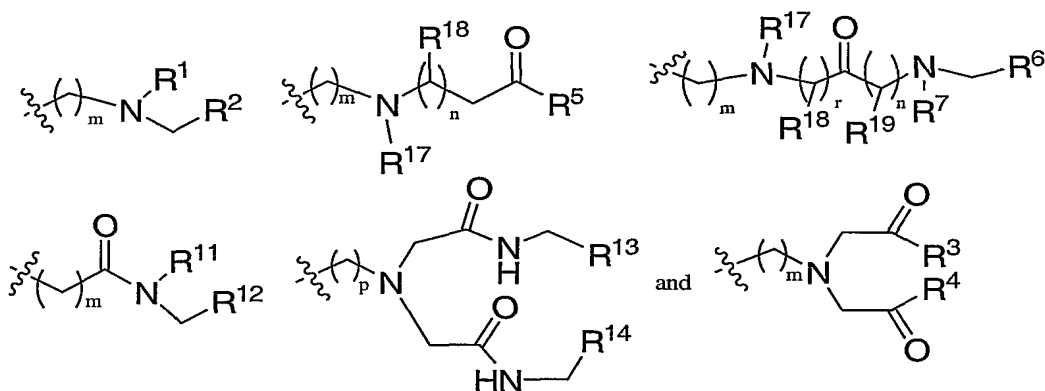
n and r are independently of each other 0, 1 or 2;

t is 1 or 2;

or a stereoisomer, enantiomer, racemate, pharmaceutically acceptable salt, solvate, hydrate or polymorph thereof.

5 In one embodiment, the substituent on the alkyl portion of R^2 to R^6 , R^8 to R^{10} and R^{12} to R^{16} is independently selected from $-NR^{20}C(=O)OR^{21}$ or $-NR^{20}SO_2R^{21}$.

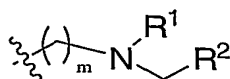
The present invention further relates to compounds represented by Formula I wherein A is selected from



10 and all of the other substituents are as described hereinabove in Formula I. In one embodiment, one or more of n, m and r is 0. In another embodiment, R^{17} is hydrogen. In another embodiment, one or more of R^{18} and R^{19} is hydrogen. In another embodiment, one or more of R^1 , R^7 and R^{11} is hydrogen.

In a particular embodiment, one or more of R^2 to R^6 and R^{12} to R^{14} is a group independently selected from substituted $-CH_2$ -phenyl, substituted $-CH_2$ -naphthyl, substituted $-CH_2$ -benzyl, substituted $-CH_2$ -cyclohexyl, substituted $-CH_2$ -quinolinyl, substituted $-CH_2$ -isoquinolinyl, substituted $-CH_2$ -pyridyl, $-CH(Ph)_2$, substituted $-CH_2CH_2$ -phenyl, substituted $-CH_2CH_2$ -naphthyl, substituted $-CH_2CH_2$ -benzyl, substituted $-CH_2CH_2$ -cyclohexyl, substituted $-CH_2CH_2$ -quinolinyl, substituted $-CH_2CH_2$ -isoquinolinyl, substituted $-CH_2CH_2$ -pyridyl, substituted $-CH_2CH(Ph)_2$, substituted methyl, substituted ethyl, substituted propyl, substituted isopropyl, substituted butyl, substituted iso-butyl, substituted sec-butyl or substituted tert-butyl, wherein the alkyl (alkyl, CH_2 or CH_2CH_2) portion of the group is substituted with a substituent that is independently selected from $-NR^{20}C(=O)R^{21}$, $-NR^{20}C(=O)OR^{21}$, $-C(=O)NR^{21}R^{22}$, $-NR^{20}SO_2R^{21}$ or $-NR^{20}C(=O)NR^{21}R^{22}$. In an embodiment, the substituent on the alkyl portion of R^2 to R^6 and R^{12} to R^{14} is on the carbon atom attached to the rest of the molecule (the first carbon atom). In one embodiment, the substituent on the alkyl portion of R^2 to R^6 and R^{12} to R^{14} is independently selected from $-NR^{20}C(=O)OR^{21}$ or $-NR^{20}SO_2R^{21}$.

In another embodiment of Formula I, A is

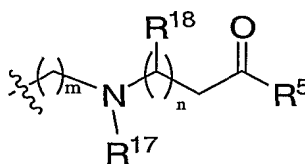


wherein R^1 and R^2 are as described above in Formula I. In one embodiment, m is 0 or 1. In a particular embodiment, R^1 is hydrogen; and R^2 is substituted C_1 - C_{10} alkylaryl.

In one embodiment, R^2 is selected from substituted $-CH_2$ -phenyl, substituted $-CH_2$ -naphthyl, substituted $-CH_2$ -benzyl, substituted $-CH_2$ -cyclohexyl, substituted $-CH_2$ -quinolinyl, substituted $-CH_2$ -isoquinolinyl, substituted $-CH_2$ -pyridyl, $-CH(Ph)_2$, substituted $-CH_2CH_2$ -phenyl, substituted $-CH_2CH_2$ -naphthyl, substituted $-CH_2CH_2$ -benzyl, substituted $-CH_2CH_2$ -cyclohexyl, substituted $-CH_2CH_2$ -quinolinyl, substituted $-CH_2CH_2$ -isoquinolinyl, substituted $-CH_2CH_2$ -pyridyl, substituted $-CH_2CH(Ph)_2$, substituted methyl, substituted ethyl, substituted propyl, substituted isopropyl, substituted butyl, substituted iso-butyl, substituted sec-butyl or substituted tert-butyl, wherein the alkyl (alkyl, CH_2 or CH_2CH_2) portion of the group is substituted with a substituent that is independently selected from $-NR^{20}C(=O)R^{21}$, $-NR^{20}C(=O)OR^{21}$, $-C(=O)NR^{21}R^{22}$, $-NR^{20}SO_2R^{21}$ or $-NR^{20}C(=O)NR^{21}R^{22}$. In one embodiment, the substituent on the alkyl portion of R^2 is on the carbon atom attached to the rest of the molecule (the first carbon atom). In a particular embodiment, R^2 is $-CH_2CH_2$ -phenyl, wherein the CH_2CH_2 is substituted with a substituent that is independently selected from $-NR^{20}C(=O)R^{21}$, $-NR^{20}C(=O)OR^{21}$, $-C(=O)NR^{21}R^{22}$, $-NR^{20}SO_2R^{21}$ or $-NR^{20}C(=O)NR^{21}R^{22}$.

In one embodiment, the substituent on the alkyl portion of R^2 is $-NR^{20}C(=O)OR^{21}$. In one embodiment R^{20} is hydrogen and R^{21} is unsubstituted or substituted C_1 - C_{10} alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted C_1 - C_{10} alkylaryl, or unsubstituted or substituted C_1 - C_{10} alkylheterocyclyl. In one embodiment R^{20} is hydrogen and R^{21} is unsubstituted or substituted C_1 - C_{10} alkyl. In one embodiment R^{20} is hydrogen and R^{21} is unsubstituted or substituted tert-butyl.

In another embodiment of Formula I, A is



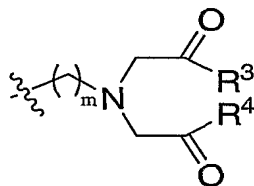
wherein R^5 , R^{17} and R^{18} are as described above in Formula I. In one embodiment, one or more of n and m is 0. In another embodiment, R^{17} is hydrogen. In another embodiment, R^{18} is hydrogen. In a particular embodiment, n and m is 0 and R^{17} is hydrogen; and R^5 is substituted C_1 - C_{10} alkylaryl.

In a particular embodiment, R^5 is selected from substituted $-CH_2$ -phenyl, substituted $-CH_2$ -naphthyl, substituted $-CH_2$ -benzyl, substituted $-CH_2$ -cyclohexyl, substituted $-CH_2$ -quinolinyl, substituted $-CH_2$ -isoquinolinyl, substituted $-CH_2$ -pyridyl, $-CH(Ph)_2$, substituted $-CH_2CH_2$ -phenyl, substituted $-CH_2CH_2$ -naphthyl, substituted $-CH_2CH_2$ -benzyl, substituted $-CH_2CH_2$ -cyclohexyl, substituted $-CH_2CH_2$ -quinolinyl, substituted $-CH_2CH_2$ -isoquinolinyl, substituted $-CH_2CH_2$ -pyridyl, substituted $-CH_2CH(Ph)_2$, substituted methyl, substituted ethyl, substituted propyl, substituted isopropyl, substituted butyl, substituted iso-butyl, substituted sec-butyl or substituted tert-butyl, wherein the alkyl (alkyl, CH_2 or

CH₂CH₂) portion of the group is substituted with a substituent that is independently selected from –NR²⁰C(=O)R²¹, –NR²⁰C(=O)OR²¹, –C(=O)NR²¹R²², –NR²⁰SO₂R²¹ or –NR²⁰C(=O)NR²¹R²². In a particular embodiment, R⁵ is –CH₂-phenyl wherein the CH₂ portion of the group is substituted with a substituent that is independently selected from –NR²⁰C(=O)R²¹, –NR²⁰C(=O)OR²¹, –C(=O)NR²¹R²², –NR²⁰SO₂R²¹ or –NR²⁰C(=O)NR²¹R²². In one embodiment, the substitution on R⁵ is on the first carbon atom.

In one embodiment, the substituent on the alkyl portion of R⁵ is –NR²⁰C(=O)OR²¹ or –NR²⁰SO₂R²¹. In one embodiment R²⁰ is hydrogen and R²¹ is unsubstituted or substituted C₁-C₁₀ alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted C₁-C₁₀ alkylaryl, or unsubstituted or substituted C₁-C₁₀ alkylheterocyclyl. In one embodiment R²⁰ is hydrogen and R²¹ is unsubstituted or substituted tert-butyl, unsubstituted or substituted phenyl, or unsubstituted or substituted –CH₂-phenyl.

In another embodiment of Formula I, A is



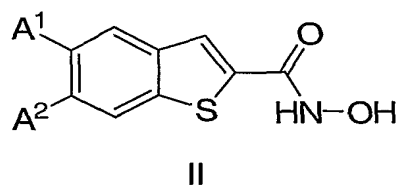
wherein R³ and R⁴ are as described above in Formula I. In one embodiment, m is 0 or 1. In a particular embodiment, R³ and R⁴ are independently selected from substituted –CH₂-phenyl, substituted –CH₂-naphthyl, substituted –CH₂-benzyl, substituted –CH₂-cyclohexyl, substituted –CH₂-quinoliny, substituted –CH₂-isoquinoliny, substituted –CH₂-pyridyl, –CH(Ph)₂, substituted –CH₂CH₂-phenyl, substituted –CH₂CH₂-naphthyl, substituted –CH₂CH₂-benzyl, substituted –CH₂CH₂-cyclohexyl, substituted –CH₂CH₂-quinoliny, substituted –CH₂CH₂-isoquinoliny, substituted –CH₂CH₂-pyridyl, substituted –CH₂CH(Ph)₂, substituted methyl, substituted ethyl, substituted propyl, substituted isopropyl, substituted butyl, substituted iso-butyl, substituted sec-butyl or substituted tert-butyl, wherein the alkyl (alkyl, CH₂ or CH₂CH₂) portion of the group is substituted with a substituent that is independently selected from –NR²⁰C(=O)R²¹, –NR²⁰C(=O)OR²¹, –C(=O)NR²¹R²², –NR²⁰SO₂R²¹ or –NR²⁰C(=O)NR²¹R²². In one embodiment, the substitution on R³ or R⁴ is on the first carbon atom. In a particular embodiment, R³ or R⁴ is –CH₂-phenyl, wherein the CH₂ is substituted with a substituent that is independently selected from –NR²⁰C(=O)R²¹, –NR²⁰C(=O)OR²¹, –C(=O)NR²¹R²², –NR²⁰SO₂R²¹ or –NR²⁰C(=O)NR²¹R²².

In one embodiment, the substituent on the alkyl portion of R³ or R⁴ is –NR²⁰C(=O)OR²¹ or –NR²⁰SO₂R²¹. In one embodiment R²⁰ is hydrogen and R²¹ is unsubstituted or substituted C₁-C₁₀ alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted

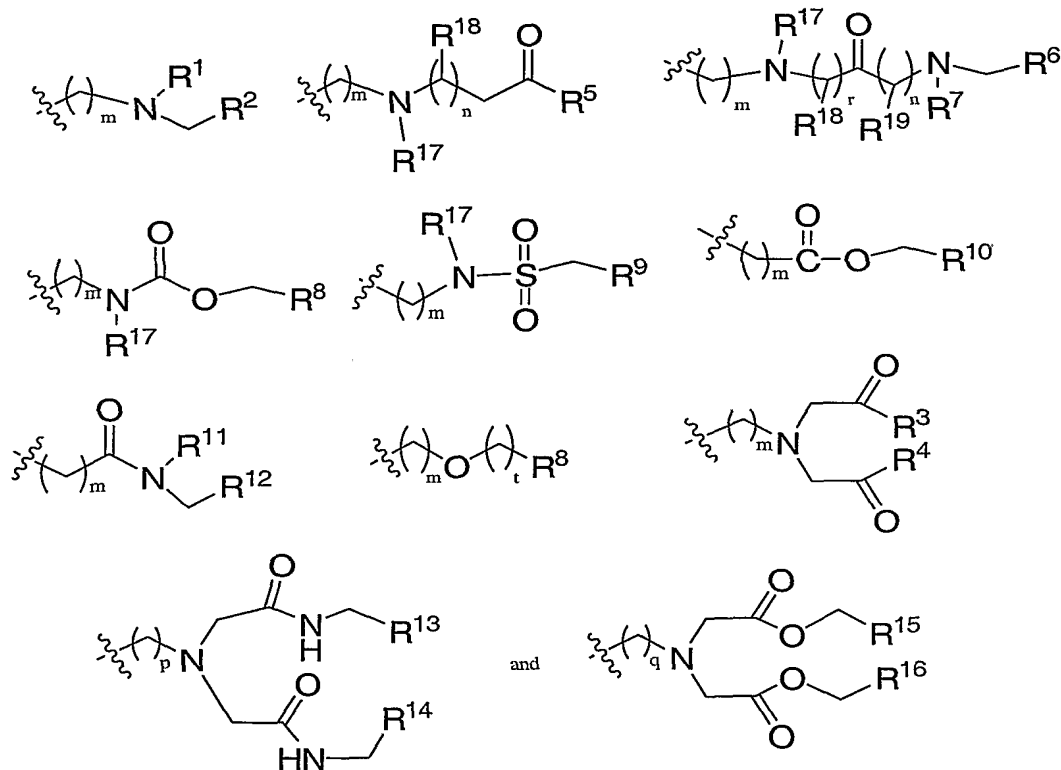
C₁-C₁₀ alkylaryl, or unsubstituted or substituted C₁-C₁₀ alkylheterocyclyl. In one embodiment R²⁰ is hydrogen and R²¹ is unsubstituted or substituted tert-butyl, unsubstituted or substituted phenyl, unsubstituted or substituted -CH₂-phenyl.

The present invention further relates to compounds represented by Formula II, i.e.,

- 5 hydroxamic acid derivatives, and/or stereoisomers (including enantiomers), racemates, pharmaceutically acceptable salts, solvates, hydrates or polymorphs thereof:



wherein one of A¹ and A² is hydrogen and the other is a group selected from



10 wherein R² to R⁶, R⁸ to R¹⁰ and R¹² to R¹⁶ are, independently of each other, a group selected from substituted C₁-C₁₀ alkyl, substituted C₁-C₁₀ alkylaryl, substituted C₁-C₁₀ alkylcycloalkyl or substituted C₁-C₁₀ alkylheterocyclyl; wherein the alkyl portion of the group is substituted with a substituent that is independently selected from -NR²⁰C(=O)R²¹, -NR²⁰C(=O)OR²¹, -C(=O)NR²¹R²², -NR²⁰SO₂R²¹ or -NR²⁰C(=O)NR²¹R²²;

15 R¹, R⁷, R¹¹ and R¹⁷ to R²⁰ are independently selected from hydrogen, unsubstituted or substituted C₁-C₁₀ alkyl, unsubstituted or substituted aryl, unsubstituted or substituted C₃-C₈ cycloalkyl,

unsubstituted or substituted heterocyclyl, unsubstituted or substituted C₁-C₁₀ alkylaryl, unsubstituted or substituted C₁-C₁₀ alkylcycloalkyl, or unsubstituted or substituted C₁-C₁₀ alkylheterocyclyl;

R²¹ is selected from unsubstituted or substituted C₁-C₁₀ alkyl, unsubstituted or substituted aryl, unsubstituted or substituted C₃-C₈ cycloalkyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted C₁-C₁₀ alkylaryl, unsubstituted or substituted C₁-C₁₀ alkylcycloalkyl, or unsubstituted or substituted C₁-C₁₀ alkylheterocyclyl;

R²² is selected from hydrogen, unsubstituted or substituted C₁-C₁₀ alkyl, unsubstituted or substituted aryl, unsubstituted or substituted C₃-C₈ cycloalkyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted C₁-C₁₀ alkylaryl, unsubstituted or substituted C₁-C₁₀ alkylcycloalkyl, or unsubstituted or substituted C₁-C₁₀ alkylheterocyclyl;

m, p and q are independently of each other 0, 1 or 2;

n and r are independently of each other 0, 1 or 2;

t is 1 or 2;

or a stereoisomer, enantiomer, racemate, pharmaceutically acceptable salt, solvate, hydrate or polymorph thereof.

The invention also encompasses compounds of Formula II wherein one of A¹ and A² have the embodiments described for A under Formula I. In one embodiment, A¹ is hydrogen.

In one embodiment, the substituent on the alkyl portion of R² to R⁶, R⁸ to R¹⁰, R¹² to R¹⁶ is independently selected from -NR²⁰C(=O)OR²¹ or -NR²⁰SO₂R²¹.

Specific embodiments depicting non-limiting Examples of the hydroxamic acid derivatives of Formula I are provided in Table 1 in the Experimental Section hereinbelow.

Specific examples of the compounds of the instant invention include:

tert-butyl [(1*S*)-1-benzyl-2-({2-[(hydroxyamino)carbonyl]-1-benzothien-6-yl}amino)ethyl]carbamate;

N-hydroxy-6-{{[[[(4-methylphenyl)sulfonyl]amino}(phenyl)acetyl]amino]-1-benzothiophene-2-carboxamide};

N-hydroxy-6-{{[[[(4-methoxyphenyl)sulfonyl]amino}(phenyl)acetyl]amino]-1-benzothiophene-2-carboxamide};

tert-butyl [(1*R*)-2-({2-[(hydroxyamino)carbonyl]-1-benzothien-6-yl}amino)-2-oxo-1-phenylethyl]carbamate;

benzyl [(1S)-2-({2-[(hydroxyamino)carbonyl]-1-benzothien-6-yl}amino)-2-oxo-1-phenylethyl]carbamate;

benzyl [(1R)-2-({2-[(hydroxyamino)carbonyl]-1-benzothien-6-yl}amino)-2-oxo-1-phenylethyl]carbamate;

5 or a pharmaceutically acceptable salt or stereoisomer thereof

Chemical Definitions

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, C₁-C₁₀, as in
10 "C₁-C₁₀ alkyl" is defined to include groups having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbons in a linear or branched arrangement. For example, "C₁-C₁₀ alkyl" specifically includes methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *i*-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, and so on. The term "cycloalkyl" means a monocyclic saturated aliphatic hydrocarbon group having the specified number of carbon atoms. For example, "cycloalkyl" includes cyclopropyl, methyl-cyclopropyl, 2,2-dimethyl-
15 cyclobutyl, 2-ethyl-cyclopentyl, cyclohexyl, and so on. In an embodiment of the invention the term "cycloalkyl" includes the groups described immediately above and further includes monocyclic unsaturated aliphatic hydrocarbon groups. For example, "cycloalkyl" as defined in this embodiment includes cyclopropyl, methyl-cyclopropyl, 2,2-dimethyl-cyclobutyl, 2-ethyl-cyclopentyl, cyclohexyl, cyclopentenyl, cyclobutenyl and so on. In an embodiment, if the number of carbon atoms is not specified,
20 "alkyl" refers to C₁-C₁₂ alkyl and in a further embodiment, "alkyl" refers to C₁-C₆ alkyl. In an embodiment, if the number of carbon atoms is not specified, "cycloalkyl" refers to C₃-C₁₀ cycloalkyl and in a further embodiment, "cycloalkyl" refers to C₃-C₇ cycloalkyl. In an embodiment, examples of "alkyl" include methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl and *i*-butyl.

The term "alkylene" means a hydrocarbon diradical group having the specified number of
25 carbon atoms. For example, "alkylene" includes -CH₂-, -CH₂CH₂- and the like. In an embodiment, if the number of carbon atoms is not specified, "alkylene" refers to C₁-C₁₂ alkylene and in a further embodiment, "alkylene" refers to C₁-C₆ alkylene.

When used in the phrases "alkylaryl", "alkylcycloalkyl" and "alkylheterocyclyl" the term "alkyl" refers to the alkyl portion of the moiety and does not describe the number of atoms in the aryl and
30 heteroaryl portion of the moiety. In an embodiment, if the number of carbon atoms is not specified, "alkyl" of "alkylaryl", "alkylcycloalkyl" and "alkylheterocyclyl" refers to C₁-C₁₂ alkyl and in a further embodiment, "aralkyl" refers to C₁-C₆ alkyl.

If no number of carbon atoms is specified, the term "alkenyl" refers to a non-aromatic hydrocarbon radical, straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one
35 carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to four

non-aromatic carbon-carbon double bonds may be present. Thus, "C₂-C₆ alkenyl" means an alkenyl radical having from 2 to 6 carbon atoms. Alkenyl groups include ethenyl, propenyl, butenyl, 2-methylbutenyl and cyclohexenyl. The straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted if a substituted alkenyl group is indicated.

5 The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Thus, "C₂-C₆ alkynyl" means an alkynyl radical having from 2 to 6 carbon atoms. Alkynyl groups include ethynyl, propynyl, butynyl, 3-methylbutynyl and so on. The straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted
10 if a substituted alkynyl group is indicated.

In certain instances, substituents may be defined with a range of carbons that includes zero, such as (C₀-C₆)alkylene-aryl. If aryl is taken to be phenyl, this definition would include phenyl itself as well as -CH₂Ph, -CH₂CH₂Ph, CH(CH₃)CH₂CH(CH₃)Ph, and so on.

15 In one embodiment, as used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl and biphenyl. In cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is via the aromatic ring.

20 In another embodiment, "aryl" is an aromatic ring of 5 to 14 carbons atoms, and includes a carbocyclic aromatic group fused with a 5-or 6-membered cycloalkyl group such as indan. Examples of carbocyclic aromatic groups include, but are not limited to, phenyl, naphthyl, e.g., 1-naphthyl and 2-naphthyl; anthracenyl, e.g., 1-anthracenyl, 2-anthracenyl; phenanthrenyl; fluorenonyl, e.g., 9-fluorenonyl, indanyl and the like. A carbocyclic aromatic group is optionally substituted with a designated number of substituents, described below.

25 The term heteroaryl, as used herein, represents a stable monocyclic or bicyclic ring of up to 7 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. In another embodiment, the term heteroaryl refers to a monocyclic, bicyclic or tricyclic aromatic ring of 5- to 14-ring atoms of carbon and from one to four heteroatoms selected from O, N, or S. Heteroaryl groups within the scope of this definition include but
30 are not limited to: acridinyl, carbazolyl, cinnolinyl, quinoxaliny, pyrazolyl, indolyl, benzotriazolyl, furanyl, thienyl, benzothieryl, benzofuranyl, quinolinyl, isoquinolinyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrahydroquinoline. As with the definition of heterocycle below, "heteroaryl" is also understood to include the N-oxide derivative of any nitrogen-containing heteroaryl. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic
35 or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively.

In another embodiment, "heteroaryl" is a monocyclic, bicyclic or tricyclic aromatic ring of 5- to 14-ring atoms of carbon and from one to four heteroatoms selected from O, N, or S. Examples of heteroaryl include, but are not limited to pyridyl, e.g., 2-pyridyl (also referred to as α -pyridyl), 3-pyridyl (also referred to as β -pyridyl) and 4-pyridyl (also referred to as γ -pyridyl); thienyl, e.g., 2-thienyl and 3-thienyl; furanyl, e.g., 2-furanyl and 3-furanyl; pyrimidyl, e.g., 2-pyrimidyl and 4-pyrimidyl; imidazolyl, e.g., 2-imidazolyl; pyranyl, e.g., 2-pyranyl and 3-pyranyl; pyrazolyl, e.g., 4-pyrazolyl and 5-pyrazolyl; thiazolyl, e.g., 2-thiazolyl, 4-thiazolyl and 5-thiazolyl; thiadiazolyl; isothiazolyl; oxazolyl, e.g., 2-oxazolyl, 4-oxazolyl and 5-oxazolyl; isoxazolyl; pyrrolyl; pyridazinyl; pyrazinyl and the like. Heterocyclic aromatic (or heteroaryl) as defined above may be optionally substituted with a designated number of substituents, as described below for aromatic groups.

In an embodiment, "heteroaryl" may also include a "fused polycyclic aromatic", which is a heteroaryl fused with one or more other heteroaryl or nonaromatic heterocyclic ring. Examples include, quinoliny and isoquinoliny, e.g., 2-quinoliny, 3-quinoliny, 4-quinoliny, 5-quinoliny, 6-quinoliny, 7-quinoliny and 8-quinoliny, 1-isoquinoliny, 3-quinoliny, 4-isoquinoliny, 5-isoquinoliny, 6-isoquinoliny, 7-isoquinoliny and 8-isoquinoliny; benzofuranyl, e.g., 2-benzofuranyl and 3-benzofuranyl; dibenzofuranyl, e.g., 2,3-dihydrobenzofuranyl; dibenzothiophenyl; benzothienyl, e.g., 2-benzothienyl and 3-benzothienyl; indolyl, e.g., 2-indolyl and 3-indolyl; benzothiazolyl, e.g., 2-benzothiazolyl; benzooxazolyl, e.g., 2-benzooxazolyl; benzimidazolyl, e.g., 2-benzimidazolyl; isoindolyl, e.g., 1-isoindolyl and 3-isoindolyl; benzotriazolyl; purinyl; thianaphthenyl, pyrazinyl and the like. Fused polycyclic aromatic ring systems may optionally be substituted with a designated number of substituents, as described herein.

The term "heterocycle" or "heterocyclyl" as used herein is intended to mean a 3- to 10-membered aromatic or nonaromatic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of O, N and S, and includes bicyclic groups. "Heterocyclyl" therefore includes the above mentioned heteroaryls, as well as dihydro and tetrathydro analogs thereof. Further examples of "heterocyclyl" include, but are not limited to the following: azetidiny, benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolaziny, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridiny, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridiny, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydroisoquinoliny, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidiny, 1,4-dioxanyl, hexahydroazepiny, piperazinyl, piperidiny, pyridin-2-onyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl,

dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidiny, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof. Attachment of a heterocyclyl substituent can occur via a carbon atom or via a heteroatom.

5 In an embodiment, "heterocycle" (also referred to herein as "heterocyclyl"), is a monocyclic, bicyclic or tricyclic saturated or unsaturated ring of 5- to 14-ring atoms of carbon and from one to four heteroatoms selected from O, N, S or P. Examples of heterocyclic rings include, but are not limited to: pyrrolidinyl, piperidinyl, morpholinyl, thiamorpholinyl, piperazinyl, dihydrofuranyl, tetrahydrofuranyl, dihydropyranyl, tetrahydrodopyranyl, dihydroquinolinyl, tetrahydroquinolinyl, 10 dihydroisoquinolinyl, tetrahydroisoquinolinyl, dihydropyrazinyl, tetrahydropyrazinyl, dihydropyridyl, tetrahydropyridyl and the like.

An "alkylaryl group" (arylalkyl) is an alkyl group substituted with an aromatic group, preferably a phenyl group. A preferred alkylaryl group is a benzyl group. Suitable aromatic groups are described herein and suitable alkyl groups are described herein. Suitable substituents for an alkylaryl 15 group are described herein.

An "alkyheterocyclyl" group" is an alkyl group substituted with a heterocyclyl group. Suitable heterocyclyl groups are described herein and suitable alkyl groups are described herein. Suitable substituents for an alkyheterocyclyl group are described herein.

An "alkycycloalkyl group" is an alkyl group substituted with a cycloalkyl group. Suitable 20 cycloalkyl groups are described herein and suitable alkyl groups are described herein. Suitable substituents for an alkycycloalkyl group are described herein.

An "aryloxy group" is an aryl group that is attached to a compound via an oxygen (e.g., phenoxy).

25 An "alkoxy group" (alkyloxy), as used herein, is a straight chain or branched C₁-C₁₂ or cyclic C₃-C₁₂ alkyl group that is connected to a compound via an oxygen atom. Examples of alkoxy groups include but are not limited to methoxy, ethoxy and propoxy.

An "arylalkoxy group" (arylalkyloxy) is an arylalkyl group that is attached to a compound via an oxygen on the alkyl portion of the arylalkyl (e.g., phenylmethoxy).

30 An "arylamino group" as used herein, is an aryl group that is attached to a compound via a nitrogen.

As used herein, an "arylalkylamino group" is an arylalkyl group that is attached to a compound via a nitrogen on the alkyl portion of the arylalkyl.

As used herein, many moieties or groups are referred to as being either "substituted or unsubstituted".

When a moiety is referred to as substituted, it denotes that any portion of the moiety that is known to one skilled in the art as being available for substitution can be substituted. The phrase "optionally substituted 35 with one or more substituents" means, in one embodiment, "zero to five substituents", and in other

embodiments, one substituent, two substituents, three substituents, four substituents or five substituents. For example, the substitutable group can be a hydrogen atom that is replaced with a group other than hydrogen (i.e., a substituent group). Multiple substituent groups can be present. When multiple substituents are present, the substituents can be the same or different and substitution can be at any of the substitutable sites. Such means for substitution are well known in the art. For purposes of exemplification, which should not be construed as limiting the scope of this invention, some examples of groups that are substituents are: alkyl groups (which can also be substituted, with one or more substituents), alkoxy groups (which can be substituted), a halogen or halo group (F, Cl, Br, I), hydroxy, nitro, oxo, -CN, -COH, -COOH, amino, azido, N-alkylamino or N,N-dialkylamino (in which the alkyl groups can also be substituted), N-aryl amino or N,N-diaryl amino (in which the aryl groups can also be substituted), esters (-C(O)-OR, where R can be a group such as alkyl, aryl, etc., which can be substituted), ureas (-NHC(O)-NHR, where R can be a group such as alkyl, aryl, etc., which can be substituted), carbamates (-NHC(O)-OR, where R can be a group such as alkyl, aryl, etc., which can be substituted), sulfonamides (-NHS(O)₂R, where R can be a group such as alkyl, aryl, etc., which can be substituted), aryl (which can be substituted), cycloalkyl (which can be substituted) alkylaryl (which can be substituted), alkylheterocyclyl (which can be substituted), alkylcycloalkyl (which can be substituted), and aryloxy.

Stereochemistry

Many organic compounds exist in optically active forms having the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these compounds, called stereoisomers, are identical except that they are non-superimposable mirror images of one another. A specific stereoisomer can also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture. Many of the compounds described herein can have one or more chiral centers and therefore can exist in different enantiomeric forms. If desired, a chiral carbon can be designated with an asterisk (*). When bonds to the chiral carbon are depicted as straight lines in the Formulas of the invention, it is understood that both the (R) and (S) configurations of the chiral carbon, and hence both enantiomers and mixtures thereof, are embraced within the Formula. As is used in the art, when it is desired to specify the absolute configuration about a chiral carbon, one of the bonds to the chiral carbon can be depicted as a wedge (bonds to atoms above the plane) and the other can be depicted as a series or wedge of short parallel lines is (bonds to atoms below the plane). The Cahn-Ingold-Prelog system can be used to assign the (R) or (S) configuration to a chiral carbon.

When the HDAC inhibitors of the present invention contain one chiral center, the compounds exist in two enantiomeric forms and the present invention includes both enantiomers and mixtures of enantiomers, such as the specific 50:50 mixture referred to as a racemic mixtures. The enantiomers can be resolved by methods known to those skilled in the art, such as formation of diastereoisomeric salts which may be separated, for example, by crystallization (see, CRC Handbook of Optical Resolutions via Diastereomeric Salt Formation by David Kozma (CRC Press, 2001)); formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic esterification; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

Designation of a specific absolute configuration at a chiral carbon of the compounds of the invention is understood to mean that the designated enantiomeric form of the compounds is in enantiomeric excess (ee) or in other words is substantially free from the other enantiomer. For example, the "R" forms of the compounds are substantially free from the "S" forms of the compounds and are, thus, in enantiomeric excess of the "S" forms. Conversely, "S" forms of the compounds are substantially free of "R" forms of the compounds and are, thus, in enantiomeric excess of the "R" forms. Enantiomeric excess, as used herein, is the presence of a particular enantiomer at greater than 50%. In a particular embodiment when a specific absolute configuration is designated, the enantiomeric excess of depicted compounds is at least about 90%.

When a compound of the present invention has two or more chiral carbons it can have more than two optical isomers and can exist in diastereoisomeric forms. For example, when there are two chiral carbons, the compound can have up to 4 optical isomers and 2 pairs of enantiomers ((S,S)/(R,R) and (R,S)/(S,R)). The pairs of enantiomers (e.g., (S,S)/(R,R)) are mirror image stereoisomers of one another. The stereoisomers that are not mirror-images (e.g., (S,S) and (R,S)) are diastereomers. The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated as described above. The present invention includes each diastereoisomer of such compounds and mixtures thereof.

As used herein, "a," "an" and "the" include singular and plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an active agent" or "a pharmacologically

active agent" includes a single active agent as well a two or more different active agents in combination, reference to "a carrier" includes mixtures of two or more carriers as well as a single carrier, and the like.

This invention is also intended to encompass pro-drugs of the hydroxamic acid derivatives disclosed herein. A prodrug of any of the compounds can be made using well-known pharmacological techniques.

This invention, in addition to the above listed compounds, is intended to encompass the use of homologs and analogs of such compounds. In this context, homologs are molecules having substantial structural similarities to the above-described compounds and analogs are molecules having substantial biological similarities regardless of structural similarities.

Pharmaceutically acceptable salts

The hydroxamic acid derivatives described herein can, as noted above, be prepared in the form of their pharmaceutically acceptable salts. Pharmaceutically acceptable salts are salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects.

Examples of such salts are (a) acid addition salts organic and inorganic acids, for example, acid addition salts which may, for example, be hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid and the like. Pharmaceutically acceptable salts can also be prepared from by treatment with inorganic bases, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine, and the like. Pharmaceutically acceptable salts can also salts formed from elemental anions such as chlorine, bromine and iodine.

The active compounds disclosed can, as noted above, also be prepared in the form of their hydrates. The term "hydrate" includes but is not limited to hemihydrate, monohydrate, dihydrate, trihydrate, tetrahydrate and the like.

The active compounds disclosed can, as noted above, also be prepared in the form of a solvate with any organic or inorganic solvent, for example alcohols such as methanol, ethanol, propanol and isopropanol, ketones such as acetone, aromatic solvents and the like.

The active compounds disclosed can also be prepared in any solid or liquid physical form. For example, the compound can be in a crystalline form, in amorphous form, and have any particle size. Furthermore, the compound particles may be micronized, or may be agglomerated, particulate granules, powders, oils, oily suspensions or any other form of solid or liquid physical form.

The compounds of the present invention may also exhibit polymorphism. This invention further includes different polymorphs of the compounds of the present invention. The term "polymorph" refers to a particular crystalline state of a substance, having particular physical properties such as X-ray diffraction, IR spectra, melting point, and the like.

As used herein, "a," "an" and "the" include singular and plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an active agent" or "a pharmacologically active agent" includes a single active agent as well as two or more different active agents in combination, reference to "a carrier" includes mixtures of two or more carriers as well as a single carrier, and the like.

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METHODS OF TREATMENT

The invention also relates to methods of using the hydroxamic acid derivatives described herein. As demonstrated herein, the hydroxamic acid derivatives of the present invention are useful for the treatment of cancer. In addition, there is a wide range of other diseases for which hydroxamic acid derivatives have been found useful. Non-limiting examples are thioredoxin (TRX)-mediated diseases as described herein, and diseases of the central nervous system (CNS) as described herein.

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1. Treatment of Cancer

As demonstrated herein, the hydroxamic acid derivatives of the present invention are useful for the treatment of cancer. Accordingly, in one embodiment, the invention relates to a method of treating cancer in a subject in need of treatment comprising administering to said subject a therapeutically effective amount of the hydroxamic acid derivatives described herein.

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The term "cancer" refers to any cancer caused by the proliferation of neoplastic cells, such as solid tumors, neoplasms, carcinomas, sarcomas, leukemias, lymphomas and the like. In particular, cancers that may be treated by the compounds, compositions and methods of the invention include, but are not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma

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(reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

In an embodiment, the instant compounds are useful in the treatment of cancers that include, but are not limited to: leukemias including acute leukemias and chronic leukemias such as acute lymphocytic leukemia (ALL), Acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML) and Hairy Cell Leukemia; lymphomas such as cutaneous T-cell lymphomas (CTCL), noncutaneous peripheral T-cell lymphomas, lymphomas associated with human T-cell lymphotropic virus (HTLV) such as adult T-cell leukemia/lymphoma (ATLL), Hodgkin's disease and non-Hodgkin's lymphomas, large-cell lymphomas, diffuse large B-cell lymphoma (DLBCL); Burkitt's lymphoma; mesothelioma, primary central nervous system (CNS) lymphoma; multiple myeloma; childhood solid tumors such as brain tumors, neuroblastoma, retinoblastoma, Wilm's tumor, bone tumors, and soft-tissue sarcomas, common solid tumors of adults such as head and neck cancers (e.g., oral, laryngeal and esophageal), genito urinary cancers (e.g., prostate, bladder, renal, uterine, ovarian, testicular, rectal and colon), lung cancer, breast cancer, pancreatic cancer, melanoma and other skin cancers, stomach cancer, brain tumors, liver cancer and thyroid cancer.

2. Treatment of thioredoxin (TRX)-mediated diseases

In another embodiment, the hydroxamic acid derivatives are used in a method of treating a thioredoxin (TRX)-mediated disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of one or more of the hydroxamic acid compounds

described herein.

Examples of TRX-mediated diseases include, but are not limited to, acute and chronic inflammatory diseases, autoimmune diseases, allergic diseases, diseases associated with oxidative stress, and diseases characterized by cellular hyperproliferation.

5 Non-limiting examples are inflammatory conditions of a joint including rheumatoid arthritis (RA) and psoriatic arthritis; inflammatory bowel diseases such as Crohn's disease and ulcerative colitis; spondyloarthropathies; scleroderma; psoriasis (including T-cell mediated psoriasis) and inflammatory dermatoses such as dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria; vasculitis (e.g., necrotizing, cutaneous, and hypersensitivity vasculitis); eosinophilic myositis, eosinophilic fasciitis; 10 cancers with leukocyte infiltration of the skin or organs, ischemic injury, including cerebral ischemia (e.g., brain injury as a result of trauma, epilepsy, hemorrhage or stroke, each of which may lead to neurodegeneration); HIV, heart failure, chronic, acute or malignant liver disease, autoimmune thyroiditis; systemic lupus erythematosus, Sjorgren's syndrome, lung diseases (e.g., ARDS); acute pancreatitis; amyotrophic lateral sclerosis (ALS); Alzheimer's disease; cachexia/anorexia; asthma; atherosclerosis; 15 chronic fatigue syndrome, fever; diabetes (e.g., insulin diabetes or juvenile onset diabetes); glomerulonephritis; graft versus host rejection (e.g., in transplantation); hemorrhagic shock; hyperalgesia; inflammatory bowel disease; multiple sclerosis; myopathies (e.g., muscle protein metabolism, esp. in sepsis); osteoporosis; Parkinson's disease; pain; pre-term labor; psoriasis; reperfusion injury; cytokine-induced toxicity (e.g., septic shock, endotoxic shock); side effects from radiation therapy, 20 temporal mandibular joint disease, tumor metastasis; or an inflammatory condition resulting from strain, sprain, cartilage damage, trauma such as burn, orthopedic surgery, infection or other disease processes. Allergic diseases and conditions, include but are not limited to respiratory allergic diseases such as asthma, allergic rhinitis, hypersensitivity lung diseases, hypersensitivity pneumonitis, eosinophilic pneumonias (e.g., Loeffler's syndrome, chronic eosinophilic pneumonia), delayed-type hypersensitivity, 25 interstitial lung diseases (ILD) (e.g., idiopathic pulmonary fibrosis, or ILD associated with rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, systemic sclerosis, Sjogren's syndrome, polymyositis or dermatomyositis); systemic anaphylaxis or hypersensitivity responses, drug allergies (e.g., to penicillin, cephalosporins), insect sting allergies, and the like.

30 3. Treatment of diseases of the central nervous system (CNS)

In another embodiment, the hydroxamic acid derivatives are used in a method of treating a disease of the central nervous system in a subject in need thereof comprising administering to the subject a therapeutically effective amount of any one or more of the hydroxamic acid compounds described herein.

35 In a particular embodiment, the CNS disease is a neurodegenerative disease. In a further embodiment, the neurodegenerative disease is an inherited neurodegenerative disease, such as those

inherited neurodegenerative diseases that are polyglutamine expansion diseases. Generally, neurodegenerative diseases can be grouped as follows:

- I. Disorders characterized by progressive dementia in the absence of other prominent neurologic signs, such as Alzheimer's disease; Senile dementia of the Alzheimer type; and Pick's disease (lobar atrophy).
- II. Syndromes combining progressive dementia with other prominent neurologic abnormalities such as A) syndromes appearing mainly in adults (e.g., Huntington's disease, Multiple system atrophy combining dementia with ataxia and/or manifestations of Parkinson's disease, Progressive supranuclear palsy (Steel-Richardson-Olszewski), diffuse Lewy body disease, and corticodentatonigral degeneration); and B) syndromes appearing mainly in children or young adults (e.g., Hallervorden-Spatz disease and progressive familial myoclonic epilepsy).
- III. Syndromes of gradually developing abnormalities of posture and movement such as paralysis agitans (Parkinson's disease), striatonigral degeneration, progressive supranuclear palsy, torsion dystonia (torsion spasm; dystonia musculorum deformans), spasmodic torticollis and other dyskinesias, familial tremor, and Gilles de la Tourette syndrome.
- IV. Syndromes of progressive ataxia such as cerebellar degenerations (e.g., cerebellar cortical degeneration and olivopontocerebellar atrophy (OPCA)); and spinocerebellar degeneration (Friedreich's ataxia and related disorders).
- V. Syndrome of central autonomic nervous system failure (Shy-Drager syndrome).
- VI. Syndromes of muscular weakness and wasting without sensory changes (motorneuron disease such as amyotrophic lateral sclerosis, spinal muscular atrophy (e.g., infantile spinal muscular atrophy (Werdnig-Hoffman), juvenile spinal muscular atrophy (Wohlfart-Kugelberg-Welander) and other forms of familial spinal muscular atrophy), primary lateral sclerosis, and hereditary spastic paraplegia).
- VII. Syndromes combining muscular weakness and wasting with sensory changes (progressive neural muscular atrophy; chronic familial polyneuropathies) such as peroneal muscular atrophy (Charcot-Marie-Tooth), hypertrophic interstitial polyneuropathy (Dejerine-Sottas), and miscellaneous forms of chronic progressive neuropathy.
- VIII. Syndromes of progressive visual loss such as pigmentary degeneration of the retina (retinitis pigmentosa), and hereditary optic atrophy (Leber's disease).

Definitions:

The term "treating" in its various grammatical forms in relation to the present invention refers to preventing (i.e., chemoprevention), curing, reversing, attenuating, alleviating, minimizing, suppressing or halting the deleterious effects of a disease state, disease progression, disease causative agent (e.g., bacteria or viruses) or other abnormal condition. For example, treatment may involve alleviating a

symptom (i.e., not necessary all symptoms) of a disease or attenuating the progression of a disease.

Because some of the inventive methods involve the physical removal of the etiological agent, the artisan will recognize that they are equally effective in situations where the inventive compound is administered prior to, or simultaneous with, exposure to the etiological agent (prophylactic treatment) and situations
5 where the inventive compounds are administered after (even well after) exposure to the etiological agent.

Treatment of cancer, as used herein, refers to partially or totally inhibiting, delaying or preventing the progression of cancer including cancer metastasis; inhibiting, delaying or preventing the recurrence of cancer including cancer metastasis; or preventing the onset or development of cancer (chemoprevention) in a mammal, for example a human.

10 As used herein, the term "therapeutically effective amount" is intended to encompass any amount that will achieve the desired therapeutic or biological effect. The therapeutic effect is dependent upon the disease or disorder being treated or the biological effect desired. As such, the therapeutic effect can be a decrease in the severity of symptoms associated with the disease or disorder and/or inhibition (partial or complete) of progression of the disease. The amount needed to elicit the therapeutic response can be
15 determined based on the age, health, size and sex of the subject. Optimal amounts can also be determined based on monitoring of the subject's response to treatment.

In the present invention, when the compounds are used to treat or prevent cancer, the desired biological response is partial or total inhibition, delay or prevention of the progression of cancer including cancer metastasis; inhibition, delay or prevention of the recurrence of cancer including cancer metastasis;
20 or the prevention of the onset or development of cancer (chemoprevention) in a mammal, for example a human.

Furthermore, in the present invention, when the compounds are used to treat and/or prevent thioredoxin (TRX)-mediated diseases and conditions, a therapeutically effective amount is an amount that regulates, for example, increases, decreases or maintains a physiologically suitable level of TRX in the
25 subject in need of treatment to elicit the desired therapeutic effect. The therapeutic effect is dependent upon the specific TRX-mediated disease or condition being treated. As such, the therapeutic effect can be a decrease in the severity of symptoms associated with the disease or disorder and/or inhibition (partial or complete) of progression of the disease or disease.

Furthermore, in the present invention, when the compounds are used to treat and/or prevent
30 diseases or disorders of the central nervous system (CNS), a therapeutically effective amount is dependent upon the specific disease or disorder being treated. As such, the therapeutic effect can be a decrease in the severity of symptoms associated with the disease or disorder and/or inhibition (partial or complete) of progression of the disease or disorder.

In addition, a therapeutically effective amount can be an amount that inhibits histone deacetylase.

35 Further, a therapeutically effective amount, can be an amount that selectively induces terminal differentiation, cell growth arrest and/or apoptosis of neoplastic cells, or an amount that induces terminal

differentiation of tumor cells.

The method of the present invention is intended for the treatment or chemoprevention of human patients with cancer. However, it is also likely that the method would be effective in the treatment of cancer in other subjects. "Subject", as used herein, refers to animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, pigs, dogs, cats, rabbits, guinea pigs, rats, mice or other bovine, ovine, equine, canine, feline, rodent or murine species.

HISTONE DEACETYLASES AND HISTONE DEACETYLASE INHIBITORS

As demonstrated herein, the hydroxamic acid derivatives of the present invention show improved activity as histone deacetylase (HDAC) inhibitors. Accordingly, in one embodiment, the invention relates to a method of inhibiting the activity of histone deacetylase comprising contacting the histone deacetylase with an effective amount of one or more of the hydroxamic acid compounds described herein.

In one embodiment, the hydroxamic acid derivatives are potent inhibitors of Class I histone deacetylases (Class I HDACs). Class I HDACs include histone deacetylase 1 (HDAC-1), histone deacetylase 2 (HDAC-2), histone deacetylase 3 (HDAC-3) and histone deacetylase 8 (HDAC-8). In a particular embodiment, the hydroxamic acid derivatives are potent inhibitors of histone deacetylase I (HDAC-1). In another embodiment, the hydroxamic acid derivatives are potent inhibitors of Class II histone deacetylases (Class II HDACs). Class II HDACs include histone deacetylase 4 (HDAC-4), histone deacetylase 5 (HDAC-5), histone deacetylase 6 (HDAC-6), histone deacetylase 7 (HDAC-7) and histone deacetylase 9 (HDAC-9).

Histone deacetylases (HDACs), as that term is used herein, are enzymes that catalyze the removal of acetyl groups from lysine residues in the amino terminal tails of the nucleosomal core histones. As such, HDACs together with histone acetyl transferases (HATs) regulate the acetylation status of histones. Histone acetylation affects gene expression and inhibitors of HDACs, such as the hydroxamic acid-based hybrid polar compound suberoylanilide hydroxamic acid (SAHA) induce growth arrest, differentiation and/or apoptosis of transformed cells *in vitro* and inhibit tumor growth *in vivo*. HDACs can be divided into three classes based on structural homology. Class I HDACs (HDACs 1, 2, 3 and 8) bear similarity to the yeast RPD3 protein, are located in the nucleus and are found in complexes associated with transcriptional co-repressors. Class II HDACs (HDACs 4, 5, 6, 7 and 9) are similar to the yeast HDA1 protein, and have both nuclear and cytoplasmic subcellular localization. Both Class I and II HDACs are inhibited by hydroxamic acid-based HDAC inhibitors, such as SAHA. Class III HDACs form a structurally distant class of NAD dependent enzymes that are related to the yeast SIR2 proteins and are not inhibited by hydroxamic acid-based HDAC inhibitors.

Histone deacetylase inhibitors or HDAC inhibitors, as that term is used herein are compounds that are capable of inhibiting the deacetylation of histones *in vivo*, *in vitro* or both. As such, HDAC inhibitors inhibit the activity of at least one histone deacetylase. As a result of inhibiting the deacetylation

of at least one histone, an increase in acetylated histone occurs and accumulation of acetylated histone is a suitable biological marker for assessing the activity of HDAC inhibitors. Therefore, procedures that can assay for the accumulation of acetylated histones can be used to determine the HDAC inhibitory activity of compounds of interest. It is understood that compounds that can inhibit histone deacetylase activity can also bind to other substrates and as such can inhibit other biologically active molecules such as enzymes. It is also to be understood that the compounds of the present invention are capable of inhibiting any of the histone deacetylases set forth above, or any other histone deacetylases.

For example, in patients receiving HDAC inhibitors, the accumulation of acetylated histones in peripheral mononuclear cells as well as in tissue treated with HDAC inhibitors can be determined against a suitable control.

HDAC inhibitory activity of a particular compound can be determined *in vitro* using, for example, an enzymatic assays which shows inhibition of at least one histone deacetylase. Further, determination of the accumulation of acetylated histones in cells treated with a particular composition can be determinative of the HDAC inhibitory activity of a compound.

Assays for the accumulation of acetylated histones are well known in the literature. See, for example, Marks, P.A. *et al.*, J. Natl. Cancer Inst., 92:1210-1215, 2000, Butler, L.M. *et al.*, Cancer Res. 60:5165-5170 (2000), Richon, V. M. *et al.*, Proc. Natl. Acad. Sci., USA, 95:3003-3007, 1998, and Yoshida, M. *et al.*, J. Biol. Chem., 265:17174-17179, 1990.

For example, an enzymatic assay to determine the activity of an HDAC inhibitor compound can be conducted as follows. Briefly, the effect of an HDAC inhibitor compound on affinity purified human epitope-tagged (Flag) HDAC1 can be assayed by incubating the enzyme preparation in the absence of substrate on ice for about 20 minutes with the indicated amount of inhibitor compound. Substrate ($[^3\text{H}]$ acetyl-labelled murine erythroleukemia cell-derived histone) can be added and the sample can be incubated for 20 minutes at 37°C in a total volume of 30 μL . The reaction can then be stopped and released acetate can be extracted and the amount of radioactivity release determined by scintillation counting. An alternative assay useful for determining the activity of an HDAC inhibitor compound is the "HDAC Fluorescent Activity Assay; Drug Discovery Kit-AK-500" available from BIOMOL Research Laboratories, Inc., Plymouth Meeting, PA.

In vivo studies can be conducted as follows. Animals, for example, mice, can be injected intraperitoneally with an HDAC inhibitor compound. Selected tissues, for example, brain, spleen, liver etc, can be isolated at predetermined times, post administration. Histones can be isolated from tissues essentially as described by Yoshida *et al.*, J. Biol. Chem. 265:17174-17179, 1990. Equal amounts of histones (about 1 μg) can be electrophoresed on 15% SDS-polyacrylamide gels and can be transferred to Hybond-P filters (available from Amersham). Filters can be blocked with 3% milk and can be probed with a rabbit purified polyclonal anti-acetylated histone H4 antibody ($\alpha\text{Ac-H4}$) and anti-acetylated histone H3 antibody ($\alpha\text{Ac-H3}$) (Upstate Biotechnology, Inc.). Levels of acetylated histone can be

visualized using a horseradish peroxidase-conjugated goat anti-rabbit antibody (1:5000) and the SuperSignal chemiluminescent substrate (Pierce). As a loading control for the histone protein, parallel gels can be run and stained with Coomassie Blue (CB).

In addition, hydroxamic acid-based HDAC inhibitors have been shown to up regulate the expression of the p21^{WAF1} gene. The p21^{WAF1} protein is induced within 2 hours of culture with HDAC inhibitors in a variety of transformed cells using standard methods. The induction of the p21^{WAF1} gene is associated with accumulation of acetylated histones in the chromatin region of this gene. Induction of p21^{WAF1} can therefore be recognized as involved in the G1 cell cycle arrest caused by HDAC inhibitors in transformed cells.

COMBINATION THERAPY

The hydroxamic acid compounds of the present invention can be administered alone or in combination with other therapies suitable for the disease or disorder being treated. Where separate dosage formulations are used, the hydroxamic acid compound and the other therapeutic agent can be administered at essentially the same time (concurrently) or at separately staggered times (sequentially). The pharmaceutical combination is understood to include all these regimens. Administration in these various ways are suitable for the present invention as long as the beneficial therapeutic effect of the hydroxamic acid compound and the other therapeutic agent are realized by the patient at substantially the same time. In an embodiment, such beneficial effect is achieved when the target blood level concentrations of each active drug are maintained at substantially the same time.

The instant compounds are also useful in combination with known therapeutic agents and anti-cancer agents. For example, instant compounds are useful in combination with known anti-cancer agents. Combinations of the presently disclosed compounds with other anti-cancer or chemotherapeutic agents are within the scope of the invention. Examples of such agents can be found in *Cancer Principles and Practice of Oncology* by V.T. Devita and S. Hellman (editors), 6th edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Such anti-cancer agents include, but are not limited to, the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors and other angiogenesis inhibitors, inhibitors of cell proliferation and survival signaling, apoptosis inducing agents, agents that interfere with cell cycle checkpoints, agents that interfere with receptor tyrosine kinases (RTKs) and cancer vaccines. The instant compounds are particularly useful when co-administered with radiation therapy.

In an embodiment, the instant compounds are also useful in combination with known anti-cancer agents including the following: estrogen receptor modulators, androgen receptor modulators,

retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, and other angiogenesis inhibitors.

“Estrogen receptor modulators” refers to compounds that interfere with or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, diethylstilbestrol, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fluoxymesterone, Ifulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

Other hormonal agents include: aromatase inhibitors (e.g., aminoglutethimide, anastrozole and tetrazole), luteinizing hormone release hormone (LHRH) analogues, ketoconazole, goserelin acetate, leuprolide, megestrol acetate and mifepristone.

“Androgen receptor modulators” refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5 α -reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

“Retinoid receptor modulators” refers to compounds which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α -difluoromethylornithine, ILX23-7553, trans-N-(4'-hydroxyphenyl) retinamide, and N-4-carboxyphenyl retinamide.

“Cytotoxic/cytostatic agents” refer to compounds which cause cell death or inhibit cell proliferation primarily by interfering directly with the cell's functioning or inhibit or interfere with cell mytosis, including alkylating agents, tumor necrosis factors, intercalators, hypoxia activatable compounds, microtubule inhibitors/microtubule-stabilizing agents, inhibitors of mitotic kinesins, inhibitors of histone deacetylase, inhibitors of kinases involved in mitotic progression, antimetabolites; biological response modifiers; hormonal/anti-hormonal therapeutic agents, haematopoietic growth factors, monoclonal antibody targeted therapeutic agents, topoisomerase inhibitors, proteasome inhibitors and ubiquitin ligase inhibitors.

Examples of cytotoxic agents include, but are not limited to, sertenef, cachectin, chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, uracil mustard, thiotepa, busulfan, carmustine, lomustine, streptozocin, tasonermin, lonidamine, carboplatin, altretamine, dacarbazine, procarbazine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine)platinum, benzylguanine, glufosfamide, GPX100,

(trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(chloro)platinum(II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, doxorubicin, daunorubicin, idarubicin, anthracenedione, bleomycin, mitomycin C, dactinomycin, plicatamycin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, and 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin (see WO 00/50032).

An example of a hypoxia activatable compound is tirapazamine.

Examples of proteasome inhibitors include but are not limited to lactacystin and bortezomib.

Examples of microtubule inhibitors/microtubule-stabilising agents include vincristine, vinblastine, vindesine, vinzolidine, vinorelbine, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincal leukoblastine, podophyllotoxins (e.g., etoposide (VP-16) and teniposide (VM-26)), paclitaxel, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl) benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, the epothilones (see for example U.S. Pat. Nos. 6,284,781 and 6,288,237) and BMS188797.

Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusin, 9-methoxy-N,N-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine-2-(6H) propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':b,7]-indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a, 5aB, 8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydroxy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexahydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-phenanthridinium, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]acridin-6-one, N-[1-[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c] quinolin-7-one, and dimesna.

Examples of inhibitors of mitotic kinesins, and in particular the human mitotic kinesin KSP, are described in PCT Publications WO 01/30768, WO 01/98278, WO 03/050,064, WO 03/050,122, WO 03/049,527, WO 03/049,679, WO 03/049,678 and WO 03/39460 and pending PCT Appl. Nos. US03/06403 (filed March 4, 2003), US03/15861 (filed May 19, 2003), US03/15810 (filed May 19,

2003), US03/18482 (filed June 12, 2003) and US03/18694 (filed June 12, 2003). In an embodiment inhibitors of mitotic kinesins include, but are not limited to inhibitors of KSP, inhibitors of MKLP1, inhibitors of CENP-E, inhibitors of MCAK, inhibitors of Kif14, inhibitors of Mphosph1 and inhibitors of Rab6-KIFL.

Examples of “histone deacetylase inhibitors” include, but are not limited to, SAHA, TSA, oxamflatin, PXD101, MG98, valproic acid and scriptaid. Further reference to other histone deacetylase inhibitors may be found in the following manuscript; Miller, T.A. et al. J. Med. Chem. 46(24):5097-5116 (2003).

“Inhibitors of kinases involved in mitotic progression” include, but are not limited to, inhibitors of aurora kinase, inhibitors of Polo-like kinases (PLK; in particular inhibitors of PLK-1), inhibitors of bub-1 and inhibitors of bub-R1. An example of an “aurora kinase inhibitor” is VX-680.

“Antiproliferative agents” includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emittefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-dihydro-benzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-fluorouracil, floxuridine, methotrexate, leucovarin, hydroxyurea, thioguanine (6-TG), mercaptopurine (6-MP), cytarabine, pentostatin, fludarabine phosphate, cladribine (2-CDA), asparaginase, gemcitabine, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabino furanosyl cytosine and 3-aminopyridine-2-carboxaldehyde thiosemicarbazone.

Examples of monoclonal antibody targeted therapeutic agents include those therapeutic agents which have cytotoxic agents or radioisotopes attached to a cancer cell specific or target cell specific monoclonal antibody. Examples include Bexxar.

“HMG-CoA reductase inhibitors” refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®; see U.S. Pat. Nos. 4,231,938, 4,294,926 and 4,319,039), simvastatin (ZOCOR®; see U.S. Pat. Nos. 4,444,784, 4,820,850 and 4,916,239), pravastatin (PRAVACHOL®; see U.S. Pat. Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589), fluvastatin (LESCOL®; see U.S. Pat. Nos. 5,354,772, 4,911,165, 4,929,437, 5,189,164, 5,118,853, 5,290,946 and 5,356,896) and atorvastatin (LIPITOR®; see U.S. Pat. Nos. 5,273,995, 4,681,893, 5,489,691 and 5,342,952). The

structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefor the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention.

"Prenyl-protein transferase inhibitor" refers to a compound which inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase).

Examples of prenyl-protein transferase inhibitors can be found in the following publications and patents: WO 96/30343, WO 97/18813, WO 97/21701, WO 97/23478, WO 97/38665, WO 98/28980, WO 98/29119, WO 95/32987, U.S. Pat. No. 5,420,245, U.S. Pat. No. 5,523,430, U.S. Pat. No. 5,532,359, U.S. Pat. No. 5,510,510, U.S. Pat. No. 5,589,485, U.S. Pat. No. 5,602,098, European Patent Publ. 0 618 221, European Patent Publ. 0 675 112, European Patent Publ. 0 604 181, European Patent Publ. 0 696 593, WO 94/19357, WO 95/08542, WO 95/11917, WO 95/12612, WO 95/12572, WO 95/10514, U.S. Pat. No. 5,661,152, WO 95/10515, WO 95/10516, WO 95/24612, WO 95/34535, WO 95/25086, WO 96/05529, WO 96/06138, WO 96/06193, WO 96/16443, WO 96/21701, WO 96/21456, WO 96/22278, WO 96/24611, WO 96/24612, WO 96/05168, WO 96/05169, WO 96/00736, U.S. Pat. No. 5,571,792, WO 96/17861, WO 96/33159, WO 96/34850, WO 96/34851, WO 96/30017, WO 96/30018, WO 96/30362, WO 96/30363, WO 96/31111, WO 96/31477, WO 96/31478, WO 96/31501, WO 97/00252, WO 97/03047, WO 97/03050, WO 97/04785, WO 97/02920, WO 97/17070, WO 97/23478, WO 97/26246, WO 97/30053, WO 97/44350, WO 98/02436, and U.S. Pat. No. 5,532,359. For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see *European J. of Cancer*, Vol. 35, No. 9, pp.1394-1401 (1999).

"Angiogenesis inhibitors" refers to compounds that inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-1/KDR (VEGFR2), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon- α , interleukin-12, erythropoietin (epoietin- α), granulocyte-CSF (filgrastin), granulocyte, macrophage-CSF (sargramostim), pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal anti-inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxygenase-2 inhibitors like celecoxib and rofecoxib (*PNAS*, Vol. 89, p. 7384 (1992); *JNCI*, Vol. 69, p. 475 (1982); *Arch. Ophthalmol.*, Vol. 108, p.573 (1990); *Anat. Rec.*, Vol. 238, p. 68 (1994); *FEBS Letters*, Vol. 372, p. 83 (1995); *Clin. Orthop.* Vol. 313, p. 76 (1995); *J.*

Mol. Endocrinol., Vol. 16, p.107 (1996); *Jpn. J. Pharmacol.*, Vol. 75, p. 105 (1997); *Cancer Res.*, Vol. 57, p. 1625 (1997); *Cell*, Vol. 93, p. 705 (1998); *Intl. J. Mol. Med.*, Vol. 2, p. 715 (1998); *J. Biol. Chem.*, Vol. 274, p. 9116 (1999)), steroidal anti-inflammatories (such as corticosteroids, mineralocorticoids, dexamethasone, prednisone, prednisolone, methylpred, betamethasone), carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl-fumagillol, thalidomide, angiostatin, troponin-1, angiotensin II antagonists (see Fernandez et al., *J. Lab. Clin. Med.* 105:141-145 (1985)), and antibodies to VEGF (see, *Nature Biotechnology*, Vol. 17, pp.963-968 (October 1999); Kim et al., *Nature*, 362, 841-844 (1993); WO 00/44777; and WO 00/61186).

Other therapeutic agents that modulate or inhibit angiogenesis and may also be used in combination with the compounds of the instant invention include agents that modulate or inhibit the coagulation and fibrinolysis systems (see review in *Clin. Chem. La. Med.* 38:679-692 (2000)). Examples of such agents that modulate or inhibit the coagulation and fibrinolysis pathways include, but are not limited to, heparin (see *Thromb. Haemost.* 80:10-23 (1998)), low molecular weight heparins and carboxypeptidase U inhibitors (also known as inhibitors of active thrombin activatable fibrinolysis inhibitor [TAFIa]) (see *Thrombosis Res.* 101:329-354 (2001)). TAFIa inhibitors have been described in PCT Publication WO 03/013,526 and U.S. Ser. No. 60/349,925 (filed January 18, 2002).

“Agents that interfere with cell cycle checkpoints” refer to compounds that inhibit protein kinases that transduce cell cycle checkpoint signals, thereby sensitizing the cancer cell to DNA damaging agents. Such agents include inhibitors of ATR, ATM, the Chk1 and Chk2 kinases and cdk and cdc kinase inhibitors and are specifically exemplified by 7-hydroxystaurosporin, flavopiridol, CYC202 (Cyclacel) and BMS-387032.

“Agents that interfere with receptor tyrosine kinases (RTKs)” refer to compounds that inhibit RTKs and therefore mechanisms involved in oncogenesis and tumor progression. Such agents include inhibitors of c-Kit, Eph, PDGF, Flt3 and c-Met. Further agents include inhibitors of RTKs shown as described by Bume-Jensen and Hunter, *Nature*, 411:355-365, 2001.

“Inhibitors of cell proliferation and survival signaling pathway” refer to pharmaceutical agents that inhibit cell surface receptors and signal transduction cascades downstream of those surface receptors. Such agents include inhibitors of inhibitors of EGFR (for example gefitinib and erlotinib), inhibitors of ERB-2 (for example trastuzumab), inhibitors of IGFR, inhibitors of CD20 (rituximab), inhibitors of cytokine receptors, inhibitors of MET, inhibitors of PI3K (for example LY294002), serine/threonine kinases (including but not limited to inhibitors of Akt such as described in (WO 03/086404, WO 03/086403, WO 03/086394, WO 03/086279, WO 02/083675, WO 02/083139, WO 02/083140 and WO 02/083138), inhibitors of Raf kinase (for example BAY-43-9006), inhibitors of MEK (for example CI-1040 and PD-098059) and inhibitors of mTOR (for example Wyeth CCI-779 and Ariad AP23573). Such agents include small molecule inhibitor compounds and antibody antagonists.

“Apoptosis inducing agents” include activators of TNF receptor family members (including the TRAIL receptors).

The invention also encompasses combinations with NSAID's which are selective COX-2 inhibitors. For purposes of this specification NSAID's which are selective inhibitors of COX-2 are defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at least 100 fold as measured by the ratio of IC₅₀ for COX-2 over IC₅₀ for COX-1 evaluated by cell or microsomal assays. Such compounds include, but are not limited to those disclosed in U.S. Pat. 5,474,995, U.S. Pat. 5,861,419, U.S. Pat. 6,001,843, U.S. Pat. 6,020,343, U.S. Pat. 5,409,944, U.S. Pat. 5,436,265, U.S. Pat. 5,536,752, U.S. Pat. 5,550,142, U.S. Pat. 5,604,260, U.S. 5,698,584, U.S. Pat. 5,710,140, WO 94/15932, U.S. Pat. 5,344,991, U.S. Pat. 5,134,142, U.S. Pat. 5,380,738, U.S. Pat. 5,393,790, U.S. Pat. 5,466,823, U.S. Pat. 5,633,272, and U.S. Pat. 5,932,598, all of which are hereby incorporated by reference.

Inhibitors of COX-2 that are particularly useful in the instant method of treatment are: 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone; and 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine; or a pharmaceutically acceptable salt thereof.

Compounds that have been described as specific inhibitors of COX-2 and are therefore useful in the present invention include, but are not limited to: parecoxib, CELEBREX[®] and BEXTRA[®] or a pharmaceutically acceptable salt thereof.

Other examples of angiogenesis inhibitors include, but are not limited to, endostatin, ukrain, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-1*H*-1,2,3-triazole-4-carboxamide, CM101, squalamine, combretastatin, RPI4610, NX31838, sulfated mannopentase phosphate, 7,7-(carbonyl-bis[imino-N-methyl-4,2-pyrrolocarbonylimino[N-methyl-4,2-pyrrole]-carbonylimino]-bis-(1,3-naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

As used above, “integrin blockers” refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_3$ integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_5$ integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_v\beta_3$ integrin and the $\alpha_v\beta_5$ integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins.

Some specific examples of tyrosine kinase inhibitors include N-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5-yl)methylidenyl]indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-

morpholinyl)propoxyl]quinazoline, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, SH268, genistein, imatinib (STI571), CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, STI571A, N-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalazinamine, and EMD121974.

Combinations with compounds other than anti-cancer compounds are also encompassed in the instant methods. For example, combinations of the instantly claimed compounds with PPAR- γ (i.e., PPAR-gamma) agonists and PPAR- δ (i.e., PPAR-delta) agonists are useful in the treatment of certain malignancies. PPAR- γ and PPAR- δ are the nuclear peroxisome proliferator-activated receptors γ and δ . The expression of PPAR- γ on endothelial cells and its involvement in angiogenesis has been reported in the literature (see *J. Cardiovasc. Pharmacol.* 1998; 31:909-913; *J. Biol. Chem.* 1999;274:9116-9121; *Invest. Ophthalmol. Vis. Sci.* 2000; 41:2309-2317). More recently, PPAR- γ agonists have been shown to inhibit the angiogenic response to VEGF in vitro; both troglitazone and rosiglitazone maleate inhibit the development of retinal neovascularization in mice. (*Arch. Ophthalmol.* 2001; 119:709-717). Examples of PPAR- γ agonists and PPAR- γ/α agonists include, but are not limited to, thiazolidinediones (such as DRF2725, CS-011, troglitazone, rosiglitazone, and pioglitazone), fenofibrate, gemfibrozil, clofibrate, GW2570, SB219994, AR-H039242, JTT-501, MCC-555, GW2331, GW409544, NN2344, KRP297, NP0110, DRF4158, NN622, GI262570, PNU182716, DRF552926, 2-[(5,7-dipropyl-3-trifluoromethyl-1,2-benzisoxazol-6-yl)oxy]-2-methylpropionic acid (disclosed in USSN 09/782,856), and 2(R)-7-(3-(2-chloro-4-(4-fluorophenoxy) phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid (disclosed in USSN 60/235,708 and 60/244,697).

Another embodiment of the instant invention is the use of the presently disclosed compounds in combination with gene therapy for the treatment of cancer. For an overview of genetic strategies to treating cancer see Hall et al (*Am J Hum Genet* 61:785-789, 1997) and Kufe et al (*Cancer Medicine*, 5th Ed, pp 876-889, BC Decker, Hamilton 2000). Gene therapy can be used to deliver any tumor suppressing gene. Examples of such genes include, but are not limited to, p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Pat. No. 6,069,134, for example), Duc-4, NF-1, NF-2, RB, WT1, BRCA1, BRCA2, a uPA/uPAR antagonist ("Adenovirus-Mediated Delivery of a uPA/uPAR Antagonist Suppresses Angiogenesis-Dependent Tumor Growth and Dissemination in Mice," *Gene Therapy*, August 1998;5(8):1105-13), and interferon gamma (*J. Immunol.* 2000;164:217-222).

The compounds of the instant invention may also be administered in combination with an inhibitor of inherent multidrug resistance (MDR), in particular MDR associated with high levels of

expression of transporter proteins. Such MDR inhibitors include inhibitors of p-glycoprotein (P-gp), such as LY335979, XR9576, OC144-093, R101922, VX853 and PSC833 (valspodar).

A compound of the present invention may be employed in conjunction with anti-emetic agents to treat nausea or emesis, including acute, delayed, late-phase, and anticipatory emesis, which may result from the use of a compound of the present invention, alone or with radiation therapy. For the prevention or treatment of emesis, a compound of the present invention may be used in conjunction with other anti-emetic agents, especially neurokinin-1 receptor antagonists, 5HT₃ receptor antagonists, such as ondansetron, granisetron, tropisetron, and zatisetron, GABAB receptor agonists, such as baclofen, a corticosteroid such as Decadron (dexamethasone), Kenalog, Aristocort, Nasalide, Preferid, Benecorten or others such as disclosed in U.S. Patent Nos. 2,789,118, 2,990,401, 3,048,581, 3,126,375, 3,929,768, 3,996,359, 3,928,326 and 3,749,712, an antidopaminergic, such as the phenothiazines (for example prochlorperazine, fluphenazine, thioridazine and mesoridazine), metoclopramide or dronabinol. In an embodiment, an anti-emesis agent selected from a neurokinin-1 receptor antagonist, a 5HT₃ receptor antagonist and a corticosteroid is administered as an adjuvant for the treatment or prevention of emesis that may result upon administration of the instant compounds.

Neurokinin-1 receptor antagonists of use in conjunction with the compounds of the present invention are fully described, for example, in U.S. Pat. Nos. 5,162,339, 5,232,929, 5,242,930, 5,373,003, 5,387,595, 5,459,270, 5,494,926, 5,496,833, 5,637,699, 5,719,147; European Patent Publication Nos. EP 0 360 390, 0 394 989, 0 428 434, 0 429 366, 0 430 771, 0 436 334, 0 443 132, 0 482 539, 0 498 069, 0 499 313, 0 512 901, 0 512 902, 0 514 273, 0 514 274, 0 514 275, 0 514 276, 0 515 681, 0 517 589, 0 520 555, 0 522 808, 0 528 495, 0 532 456, 0 533 280, 0 536 817, 0 545 478, 0 558 156, 0 577 394, 0 585 913, 0 590 152, 0 599 538, 0 610 793, 0 634 402, 0 686 629, 0 693 489, 0 694 535, 0 699 655, 0 699 674, 0 707 006, 0 708 101, 0 709 375, 0 709 376, 0 714 891, 0 723 959, 0 733 632 and 0 776 893; PCT International Patent Publication Nos. WO 90/05525, 90/05729, 91/09844, 91/18899, 92/01688, 92/06079, 92/12151, 92/15585, 92/17449, 92/20661, 92/20676, 92/21677, 92/22569, 93/00330, 93/00331, 93/01159, 93/01165, 93/01169, 93/01170, 93/06099, 93/09116, 93/10073, 93/14084, 93/14113, 93/18023, 93/19064, 93/21155, 93/21181, 93/23380, 93/24465, 94/00440, 94/01402, 94/02461, 94/02595, 94/03429, 94/03445, 94/04494, 94/04496, 94/05625, 94/07843, 94/08997, 94/10165, 94/10167, 94/10168, 94/10170, 94/11368, 94/13639, 94/13663, 94/14767, 94/15903, 94/19320, 94/19323, 94/20500, 94/26735, 94/26740, 94/29309, 95/02595, 95/04040, 95/04042, 95/06645, 95/07886, 95/07908, 95/08549, 95/11880, 95/14017, 95/15311, 95/16679, 95/17382, 95/18124, 95/18129, 95/19344, 95/20575, 95/21819, 95/22525, 95/23798, 95/26338, 95/28418, 95/30674, 95/30687, 95/33744, 96/05181, 96/05193, 96/05203, 96/06094, 96/07649, 96/10562, 96/16939, 96/18643, 96/20197, 96/21661, 96/29304, 96/29317, 96/29326, 96/29328, 96/31214, 96/32385, 96/37489, 97/01553, 97/01554, 97/03066, 97/08144, 97/14671, 97/17362, 97/18206, 97/19084, 97/19942 and 97/21702; and in British Patent Publication Nos. 2 266 529, 2 268 931, 2 269 170, 2 269 590, 2 271 774, 2 292 144, 2 293 168, 2 293 169, and 2 302 689. The preparation of such

compounds is fully described in the aforementioned patents and publications, which are incorporated herein by reference.

In an embodiment, the neurokinin-1 receptor antagonist for use in conjunction with the compounds of the present invention is selected from: 2-(R)-(1-(R)-(3,5-
5 bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine, or a pharmaceutically acceptable salt thereof, which is described in U.S. Pat. No. 5,719,147.

10 A compound of the instant invention may also be administered with an agent useful in the treatment of anemia. Such an anemia treatment agent is, for example, a continuous erythropoiesis receptor activator (such as epoetin alfa).

A compound of the instant invention may also be administered with an agent useful in the treatment of neutropenia. Such a neutropenia treatment agent is, for example, a hematopoietic growth factor which regulates the production and function of neutrophils such as a human granulocyte colony stimulating factor, (G-CSF). Examples of a G-CSF include filgrastim.

15 A compound of the instant invention may also be administered with an immunologic-enhancing drug, such as levamisole, bacillus Calmette-Guerin, octreotide, isoprinosine and Zadaxin.

A compound of the instant invention may also be useful for treating or preventing cancer, including bone cancer, in combination with bisphosphonates (understood to include bisphosphonates, diphosphonates, bisphosphonic acids and diphosphonic acids). Examples of bisphosphonates include but
20 are not limited to: etidronate (Didronel), pamidronate (Aredia), alendronate (Fosamax), risedronate (Actonel), zoledronate (Zometa), ibandronate (Boniva), incadronate or cimadronate, clodronate, EB-1053, minodronate, neridronate, piridronate and tiludronate including any and all pharmaceutically acceptable salts, derivatives, hydrates and mixtures thereof.

25 A compound of the instant invention may also be useful for treating or preventing breast cancer in combination with aromatase inhibitors. Examples of aromatase inhibitors include but are not limited to: anastrozole, letrozole and exemestane.

A compound of the instant invention may also be useful for treating or preventing cancer in combination with siRNA therapeutics.

30 A compound of the instant invention may also be useful for treating or preventing cancer in combination with compounds which induce terminal differentiation of the neoplastic cells. Suitable differentiation agents include the compounds disclosed in any one or more of the following references, the contents of which are incorporated by reference herein.

a) Polar compounds (Marks et al (1987); , Friend, C., Scher, W., Holland, J. W., and Sato, T. (1971) *Proc. Natl. Acad. Sci. (USA)* 68: 378-382; Tanaka, M., Levy, J., Terada, M., Breslow, R.,
35 Rifkind, R. A., and Marks, P. A. (1975) *Proc. Natl. Acad. Sci. (USA)* 72: 1003-1006; Reuben, R. C.,

Wife, R. L., Breslow, R., Rifkind, R. A., and Marks, P. A. (1976) *Proc. Natl. Acad. Sci. (USA)* 73: 862-866);

b) Derivatives of vitamin D and retinoic acid (Abe, E., Miyaura, C., Sakagami, H., Takeda, M., Konno, K., Yamazaki, T., Yoshika, S., and Suda, T. (1981) *Proc. Natl. Acad. Sci. (USA)* 78: 4990-4994; Schwartz, E. L., Snoddy, J. R., Kreutter, D., Rasmussen, H., and Sartorelli, A. C. (1983) *Proc. Am. Assoc. Cancer Res.* 24: 18; Tanenaga, K., Hozumi, M., and Sakagami, Y. (1980) *Cancer Res.* 40: 914-919);

c) Steroid hormones (Lotem, J. and Sachs, L. (1975) *Int. J. Cancer* 15: 731-740);

d) Growth factors (Sachs, L. (1978) *Nature (Lond.)* 274: 535, Metcalf, D. (1985) *Science*, 229: 16-22);

e) Proteases (Scher, W., Scher, B. M., and Waxman, S. (1983) *Exp. Hematol.* 11: 490-498; Scher, W., Scher, B. M., and Waxman, S. (1982) *Biochem. & Biophys. Res. Comm.* 109: 348-354);

f) Tumor promoters (Huberman, E. and Callahan, M. F. (1979) *Proc. Natl. Acad. Sci. (USA)* 76: 1293-1297; Lottem, J. and Sachs, L. (1979) *Proc. Natl. Acad. Sci. (USA)* 76: 5158-5162); and

g) inhibitors of DNA or RNA synthesis (Schwartz, E. L. and Sartorelli, A. C. (1982) *Cancer Res.* 42: 2651-2655, Terada, M., Epner, E., Nudel, U., Salmon, J., Fibach, E., Rifkind, R. A., and Marks, P. A. (1978) *Proc. Natl. Acad. Sci. (USA)* 75: 2795-2799; Morin, M. J. and Sartorelli, A. C. (1984) *Cancer Res.* 44: 2807-2812; Schwartz, E. L., Brown, B. J., Nierenberg, M., Marsh, J. C., and Sartorelli, A. C. (1983) *Cancer Res.* 43: 2725-2730; Sugano, H., Furusawa, M., Kawaguchi, T., and Ikawa, Y. (1973) *Bibl. Hematol.* 39: 943-954; Ebert, P. S., Wars, I., and Buell, D. N. (1976) *Cancer Res.* 36: 1809-1813; Hayashi, M., Okabe, J., and Hozumi, M. (1979) *Gann* 70: 235-238).

A compound of the instant invention may also be useful for treating or preventing cancer in combination with γ -secretase inhibitors.

Also included in the scope of the claims is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of Formula I in combination with radiation therapy and/or in combination with a second compound selected from: an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxiccytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, PPAR- γ agonists, PPAR- δ agonists, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, a bisphosphonate, an aromatase inhibitor, an siRNA therapeutic, γ -secretase inhibitors, agents that interfere with receptor tyrosine kinases (RTKs) and an agent that interferes with a cell cycle checkpoint.

The use of all of these approaches in combination with the hydroxamic acid compounds described herein are within the scope of the present invention.

DOSAGES AND DOSING SCHEDULES

The dosage regimen utilizing the hydroxamic acid derivatives of the present invention can be selected in accordance with a variety of factors including type, species, age, weight, sex and the type of cancer being treated; the severity (i.e., stage) of the disease to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to treat, for example, to prevent, inhibit (fully or partially) or arrest the progress of the disease.

For oral administration, suitable daily dosages are for example between about 5-4000 mg/m² administered orally once-daily, twice-daily or three times-daily, continuous (every day) or intermittently (e.g., 3-5 days a week). For example, when used to treat the desired disease, the dose of the hydroxamic acid can range between about 2 mg to about 2000 mg per day.

The hydroxamic acid derivative is administered once daily (QD), or divided into multiple daily doses such as twice daily (BID), and three times daily (TID). For administration once a day, a suitably prepared medicament would therefore contain all of the needed daily dose. For administration twice a day, a suitably prepared medicament would therefore contain half of the needed daily dose. For administration three times a day, a suitably prepared medicament would therefore contain one third of the needed daily dose.

In addition, the administration can be continuous, i.e., every day, or intermittently. The terms "intermittent" or "intermittently" as used herein means stopping and starting at either regular or irregular intervals. For example, intermittent administration of an HDAC inhibitor may be administration one to six days per week or it may mean administration in cycles (e.g., daily administration for two to eight consecutive weeks, then a rest period with no administration for up to one week) or it may mean administration on alternate days.

Typically, an intravenous formulation may be prepared which contains a concentration of the hydroxamic acid derivative of between about 1.0 mg/mL to about 10 mg/mL. In one example, a sufficient volume of intravenous formulation can be administered to a patient in a day such that the total dose for the day is between about 10 and about 1500 mg/m².

Subcutaneous formulations, preferably prepared according to procedures well known in the art at a pH in the range between about 5 and about 12, also include suitable buffers and isotonicity agents, as described below. They can be formulated to deliver a daily dose of HDAC inhibitor in one or more daily subcutaneous administrations, e.g., one, two or three times each day.

The compounds can also be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of

ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regime.

It should be apparent to a person skilled in the art that the various modes of administration, dosages and dosing schedules described herein merely set forth specific embodiments and should not be construed as limiting the broad scope of the invention. Any permutations, variations and combinations of the dosages and dosing schedules are included within the scope of the present invention.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

PHARMACEUTICAL COMPOSITIONS

The compounds of the invention, and derivatives, fragments, analogs, homologs pharmaceutically acceptable salts or hydrate thereof, can be incorporated into pharmaceutical compositions suitable for oral administration, together with a pharmaceutically acceptable carrier or excipient. Such compositions typically comprise a therapeutically effective amount of any of the compounds above, and a pharmaceutically acceptable carrier. Preferably, the effective amount is an amount effective to selectively induce terminal differentiation of suitable neoplastic cells and less than an amount which causes toxicity in a patient.

Any inert excipient that is commonly used as a carrier or diluent may be used in the formulations of the present invention, such as for example, a gum, a starch, a sugar, a cellulosic material, an acrylate, or mixtures thereof. A preferred diluent is microcrystalline cellulose. The compositions may further comprise a disintegrating agent (e.g., croscarmellose sodium) and a lubricant (e.g., magnesium stearate), and in addition may comprise one or more additives selected from a binder, a buffer, a protease inhibitor, a surfactant, a solubilizing agent, a plasticizer, an emulsifier, a stabilizing agent, a viscosity increasing agent, a sweetener, a film forming agent, or any combination thereof. Furthermore, the compositions of the present invention may be in the form of controlled release or immediate release formulations.

In one embodiment, the pharmaceutical compositions are administered orally, and are thus

formulated in a form suitable for oral administration, i.e., as a solid or a liquid preparation. Suitable solid oral formulations include tablets, capsules, pills, granules, pellets and the like. Suitable liquid oral formulations include solutions, suspensions, dispersions, emulsions, oils and the like. In one embodiment of the present invention, the composition is formulated in a capsule. In accordance with this embodiment, the compositions of the present invention comprise in addition to the hydroxamic acid derivative active compound and the inert carrier or diluent, a hard gelatin capsule.

As used herein, "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration, such as sterile pyrogen-free water. Suitable carriers are described in the most recent edition of Remington's Pharmaceutical Sciences, a standard reference text in the field, which is incorporated herein by reference. Preferred examples of such carriers or diluents include, but are not limited to, water, saline, finger's solutions, dextrose solution, and 5% human serum albumin. Liposomes and non-aqueous vehicles such as fixed oils may also be used. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

Solid carriers/diluents include, but are not limited to, a gum, a starch (e.g., corn starch, pregelatinized starch), a sugar (e.g., lactose, mannitol, sucrose, dextrose), a cellulosic material (e.g., microcrystalline cellulose), an acrylate (e.g., polymethylacrylate), calcium carbonate, magnesium oxide, talc, or mixtures thereof.

For liquid formulations, pharmaceutically acceptable carriers may be aqueous or non-aqueous solutions, suspensions, emulsions or oils. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Examples of oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, mineral oil, olive oil, sunflower oil, and fish-liver oil. Solutions or suspensions can also include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide.

In addition, the compositions may further comprise binders (e.g., acacia, cornstarch, gelatin, carbomer, ethyl cellulose, guar gum, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, povidone), disintegrating agents (e.g., cornstarch, potato starch, alginic acid, silicon dioxide,

croscarmellose sodium, crospovidone, guar gum, sodium starch glycolate, Primogel), buffers (e.g., tris-HCl, acetate, phosphate) of various pH and ionic strength, additives such as albumin or gelatin to prevent absorption to surfaces, detergents (e.g., Tween 20, Tween 80, Pluronic F68, bile acid salts), protease inhibitors, surfactants (e.g., sodium lauryl sulfate), permeation enhancers, solubilizing agents (e.g., glycerol, polyethylene glycerol), a glidant (e.g., colloidal silicon dioxide), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite, butylated hydroxyanisole), stabilizers (e.g., hydroxypropyl cellulose, hydroxypropylmethyl cellulose), viscosity increasing agents (e.g., carbomer, colloidal silicon dioxide, ethyl cellulose, guar gum), sweeteners (e.g., sucrose, aspartame, citric acid), flavoring agents (e.g., peppermint, methyl salicylate, or orange flavoring), preservatives (e.g., Thimerosal, benzyl alcohol, parabens), lubricants (e.g., stearic acid, magnesium stearate, polyethylene glycol, sodium lauryl sulfate), flow-aids (e.g., colloidal silicon dioxide), plasticizers (e.g., diethyl phthalate, triethyl citrate), emulsifiers (e.g., carbomer, hydroxypropyl cellulose, sodium lauryl sulfate), polymer coatings (e.g., poloxamers or poloxamines), coating and film forming agents (e.g., ethyl cellulose, acrylates, polymethacrylates) and/or adjuvants.

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

It is especially advantageous to formulate oral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

The compounds of the present invention may be administered intravenously on the first day of treatment, with oral administration on the second day and all consecutive days thereafter.

The compounds of the present invention may be administered for the purpose of preventing disease progression or stabilizing tumor growth.

The preparation of pharmaceutical compositions that contain an active component is well understood in the art, for example, by mixing, granulating, or tablet-forming processes. The active
5 therapeutic ingredient is often mixed with excipients that are pharmaceutically acceptable and compatible with the active ingredient. For oral administration, the active agents are mixed with additives customary for this purpose, such as vehicles, stabilizers, or inert diluents, and converted by customary methods into suitable forms for administration, such as tablets, coated tablets, hard or soft gelatin capsules, aqueous, alcoholic or oily solutions and the like as detailed above.

10 The amount of the compound administered to the patient is less than an amount that would cause toxicity in the patient. In the certain embodiments, the amount of the compound that is administered to the patient is less than the amount that causes a concentration of the compound in the patient's plasma to equal or exceed the toxic level of the compound. Preferably, the concentration of the compound in the patient's plasma is maintained at about 10 nM. In another embodiment, the concentration of the
15 compound in the patient's plasma is maintained at about 25 nM. In another embodiment, the concentration of the compound in the patient's plasma is maintained at about 50 nM. In another embodiment, the concentration of the compound in the patient's plasma is maintained at about 100 nM. In another embodiment, the concentration of the compound in the patient's plasma is maintained at about 500 nM. In another embodiment, the concentration of the compound in the patient's plasma is maintained at about
20 1000 nM. In another embodiment, the concentration of the compound in the patient's plasma is maintained at about 2500 nM. In another embodiment, the concentration of the compound in the patient's plasma is maintained at about 5000 nM. The optimal amount of the compound that should be administered to the patient in the practice of the present invention will depend on the particular compound used and the type of cancer being treated.

25 The instant invention also includes a pharmaceutical composition useful for treating or preventing cancer that comprises a therapeutically effective amount of a compound of Formula I and a second compound selected from: an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase
30 inhibitor, an angiogenesis inhibitor, a PPAR- γ agonist, a PPAR- δ agonist, an inhibitor of cell proliferation and survival signaling, a bisphosphonate, an aromatase inhibitor, an siRNA therapeutic, γ -secretase inhibitors, agents that interfere with receptor tyrosine kinases (RTKs) and an agent that interferes with a cell cycle checkpoint.

35 In Vitro METHODS:

The present invention also provides methods of using the hydroxamic acid derivatives of the

present invention for inducing terminal differentiation, cell growth arrest and/or apoptosis of neoplastic cells thereby inhibiting the proliferation of such cells. The methods can be practiced *in vivo* or *in vitro*.

In one embodiment, the present invention provides *in vitro* methods for selectively inducing terminal differentiation, cell growth arrest and/or apoptosis of neoplastic cells, thereby inhibiting proliferation of such cells, by contacting the cells with an effective amount of any one or more of the hydroxamic acid derivatives described herein.

In a particular embodiment, the present invention relates to an *in vitro* method of selectively inducing terminal differentiation of neoplastic cells and thereby inhibiting proliferation of such cells. The method comprises contacting the cells under suitable conditions with an effective amount of one or more of the hydroxamic acid compounds described herein.

In another embodiment, the invention relates to an *in vitro* method of selectively inducing cell growth arrest of neoplastic cells and thereby inhibiting proliferation of such cells. The method comprises contacting the cells under suitable conditions with an effective amount of one or more of the hydroxamic acid compounds described herein.

In another embodiment, the invention relates to an *in vitro* method of selectively inducing apoptosis of neoplastic cells and thereby inhibiting proliferation of such cells. The method comprises contacting the cells under suitable conditions with an effective amount of one or more of the hydroxamic acid compounds described herein.

In another embodiment, the invention relates to an *in vitro* method of inducing terminal differentiation of tumor cells in a tumor comprising contacting the cells with an effective amount of any one or more of the hydroxamic acid compounds described herein.

Although the methods of the present invention can be practiced *in vitro*, it is contemplated that the preferred embodiment for the methods of selectively inducing terminal differentiation, cell growth arrest and/or apoptosis of neoplastic cells, and of inhibiting HDAC will comprise contacting the cells *in vivo*, i.e., by administering the compounds to a subject harboring neoplastic cells or tumor cells in need of treatment.

Thus, the present invention provides *in vivo* methods for selectively inducing terminal differentiation, cell growth arrest and/or apoptosis of neoplastic cells in a subject, thereby inhibiting proliferation of such cells in the subject, by administering to the subject an effective amount of any one or more of the hydroxamic acid derivatives described herein.

In a particular embodiment, the present invention relates to a method of selectively inducing terminal differentiation of neoplastic cells and thereby inhibiting proliferation of such cells in a subject. The method comprises administering to the subject an effective amount of one or more of the hydroxamic acid derivatives described herein.

In another embodiment, the invention relates to a method of selectively inducing cell growth arrest of neoplastic cells and thereby inhibiting proliferation of such cells in a subject. The method

comprises administering to the subject an effective amount of one or more of the hydroxamic acid derivatives described herein.

In another embodiment, the invention relates to a method of selectively inducing apoptosis of neoplastic cells and thereby inhibiting proliferation of such cells in a subject. The method comprises administering to the subject an effective amount of one or more of the hydroxamic acid derivatives described herein.

In another embodiment, the invention relates to a method of treating a patient having a tumor characterized by proliferation of neoplastic cells. The method comprises administering to the patient one or more of the hydroxamic acid derivatives described herein. The amount of compound is effective to selectively induce terminal differentiation, induce cell growth arrest and/or induce apoptosis of such neoplastic cells and thereby inhibit their proliferation.

The invention is illustrated in the examples in the Experimental Details Section that follows. This section is set forth to aid in an understanding of the invention but is not intended to, and should not be construed to limit in any way the invention as set forth in the claims which follow thereafter.

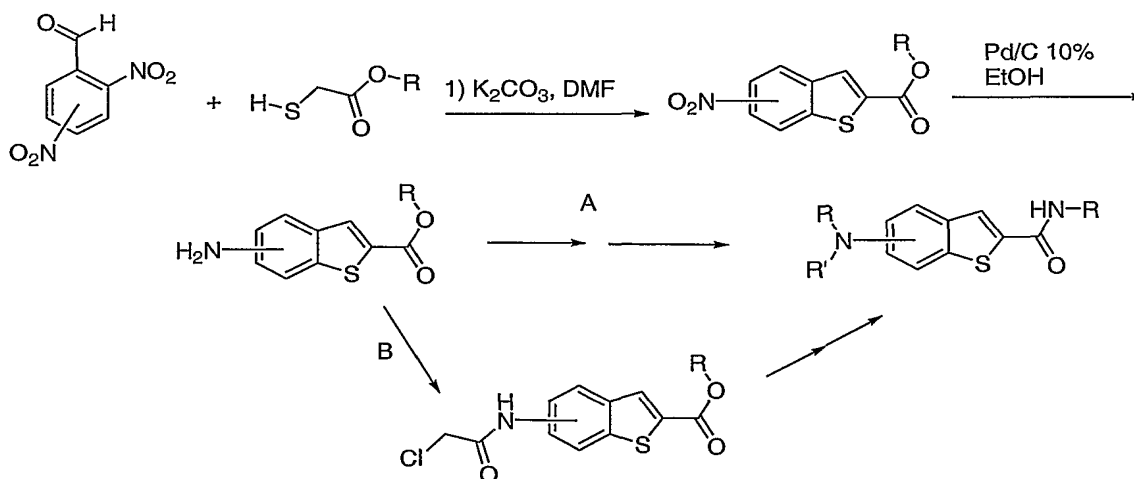
EXPERIMENTAL DETAILS SECTION

The compounds of the present invention were prepared by the general methods outlined in the synthetic schemes below, as exemplified below.

EXAMPLE 1 - SYNTHESIS

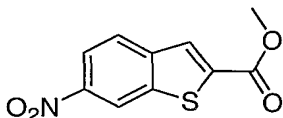
The compounds of the present invention were prepared by the general methods outlined in the synthetic schemes below, as exemplified below.

A1. 5&6-Aminobenzothiophenes. Scheme 1 illustrates the synthesis of amide, sulphonamide, urea, and alkylated amine benzothiophene derivatives from 5- and 6-amino-benzothiophenes.

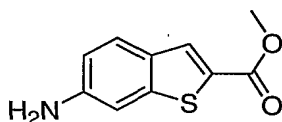


Scheme 1

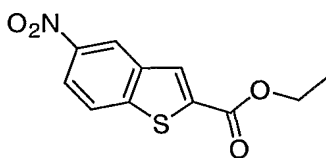
Procedures for A1. Aminobenzothiophenes.

Procedure to 6-aminobenzo[b]thiophene.

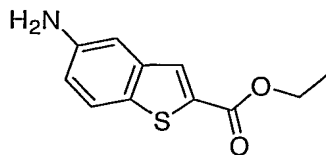
6-Nitro-benzo[b]thiophene-2-carboxylic acid methyl ester. To a mixture of 2,4-dinitrobenzaldehyde (6.45 g, 32.9 mmol) and K_2CO_3 (5.45 g, 39.4 mmol) in DMF (60 mL) was slowly added methyl thioglycolate (3.0 mL, 32.9 mmol). The mixture was stirred at RT for 1h, then at 50°C for 2h. The resultant mixture was poured into H_2O /ice and stirred until a precipitate formed. The solid was filtered and triturated with hot MeOH. The pale brown solid was filtered. 1H NMR ($DMSO-d_6$) δ 9.13 (s, 1H), 8.33 (s, 1H), 8.30-8.17 (m, 2H), 3.89 (s, 3H). MS (EI): cal'd (MH^+) 238.01, exp (MH^+) 238.10.



6-Amino-benzo[b]thiophene-2-carboxylic acid methyl ester. To a stirring solution of 6-nitro-benzo[b]thiophene-2-carboxylic acid methyl ester (3.9 g, 15.8 mmol) in DMF (120 mL) was added 10% Pd/C (700 mg, 10 wt%). The reaction was charged with H_2 , degassed and refilled with hydrogen three times. The slurry was stirred at RT for 4 days at balloon pressure, then filtered through a plug of Celite, and solvent was removed under reduced pressure. The solid was washed with EtOAc, and filtered to yield the desired amine. 1H NMR ($CDCl_3$) δ 7.92 (s, 1H), 7.65 (d, $J = 8.4$ Hz, 1H), 7.08 (s, 1H), 6.78 (d, $J = 8.4$ Hz, 1H), 3.92 (s, 3H). MS (EI): cal'd (MH^+) 208.04, exp (MH^+) 208.1.

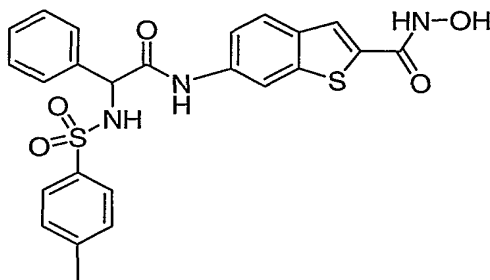


5-Nitro-benzo[b]thiophene-2-carboxylic acid ethyl ester. To a solution of 2-chloro-5-nitro-benzaldehyde (31.01 g, 167.1 mmol) in 330 mL of anhydrous DMF at 0 °C was added K_2CO_3 (27.80 g, 201.1 mmol), followed by slow addition of mercapto-acetic acid ethyl ester (18.5 mL, 168.7mmol). After stirring at 0 °C for 20 min, the resulting mixture was allowed to warm to rt and stir at rt overnight. The reaction mixture was then poured into 1.5 L of water. The solid formed was filtered and washed with 600 mL of water. After drying, 5-nitro-benzo[b]thiophene-2-carboxylic acid ethyl ester was obtained as pale solid. MS (EI): cal'd (MH^+) 252.0, exp 252.1 (MH^+).



5-Amino-benzo[b]thiophene-2-carboxylic acid ethyl ester. A suspension of 5-nitro-benzo[b]thiophene-2-carboxylic acid ethyl ester (10.52 g, 41.89 mmol) and 10% Pd/C (1.1 g) in 450 mL of EtOH was hydrogenated under 1 atm of H₂ for 4 d at rt. The reaction mixture was filtered and the filtrate was concentrated and dried to give 5-amino-benzo[b]thiophene-2-carboxylic acid ethyl ester as a green solid. A parallel reaction was preformed on 10.61 g of 5-nitro-benzo[b]thiophene-2-carboxylic acid ethyl ester in the same manner. A total of 18.37 g of 5-amino-benzo[b]thiophene-2-carboxylic acid ethyl ester was obtained. MS (EI): cal'd 222.0 (MH⁺), exp 222.2 (MH⁺).

10 Procedure for acylation

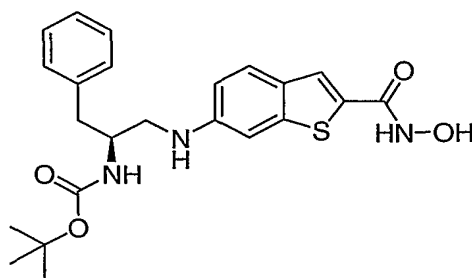


N-hydroxy-6-[[[(4-methylphenyl)sulfonyl]amino}(phenyl)acetyl]amino]-1-benzothiophene-2-

carboxamide. To a solution of {[(4-methylphenyl)sulfonyl]-amino}(phenyl)acetic acid (177 mg, 0.58 mmol), EDCI (139 mg, 0.724 mmol), HOBT (98 mg, 0.724 mmol), and DMAP (cat.) in DMF (3 mL), which was stirred for 30 min, was added a solution of 6-amino-benzo[b]thiophene-2-carboxylic acid methyl ester (100 mg, 0.480 mmol) in DMF (1 mL). After 18 h, an additional molar equivalent of acid, EDCI and HOBT were added the reaction mixture. After 24h, the solvent was removed and reaction mixture was diluted with EtOAc. The organic layer was washed with sat'd NaHCO₃, dried (Na₂SO₄), and concentrated. The residue was triturated with EtOAc and H₂O to provide a solid, which was filtered (69.6 mg, 29.2%) and used without further purification. To a solution of the methyl ester (60 mg, 0.12 mmol) in DMF/DMA (2/1 mL) was added NH₂OH (50% aq., 1 mL). The solution was stirred until the disappearance of starting material. After removal of solvent, EtOAc/MeOH/H₂O were added until a precipitate formed. The solid was filtered yielding the desired amide (38.6 mg, 64.3%). ¹H NMR (600 mHz, DMSO-d₆) δ 11.35 (br s, 1H), 10.38 (s, 1H), 9.18 (br s, 1H), 8.66 (br d, J = 1.0 Hz, 1H), 8.01 (s, 1H), 7.74 (m, 2H), 7.57 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.24-7.17 (m, 3H), 7.13 (d, J = 8.0 Hz, 2H), 5.11 (br d, J = 1.0 Hz, 1H), 2.10 (s, 3H). MS: cal'd (MH⁺) 495, exp (MH⁺) 495.

Additional analogs were prepared in procedures similar to those described for the preparation of the above *N*-hydroxy-6-[[[(4-methylphenyl)sulfonyl]amino}(phenyl)acetyl]amino]-1-benzothiophene-2-carboxamide.

5 Procedure for Formation of the Alkylated Amines



***tert*-butyl[(1*S*)-1-benzyl-2-({2-[(hydroxyamino)carbonyl]-1-benzothien-6-yl}amino)ethyl]carbamate.**

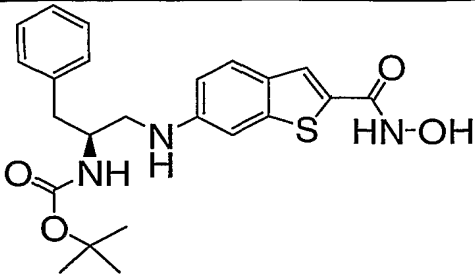
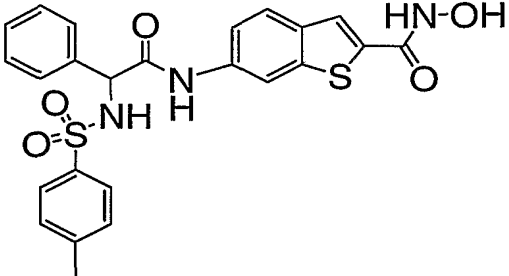
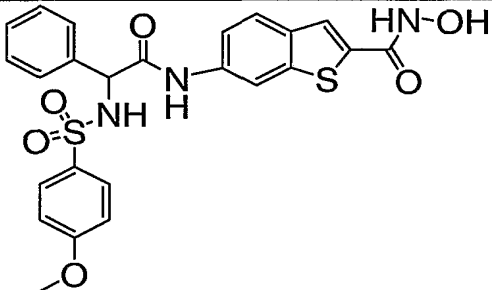
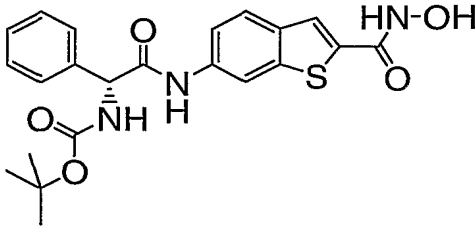
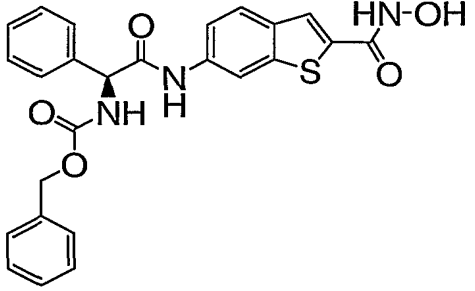
A mixture of methyl 6-amino-1-benzothiophene-2-carboxylate (300 mg, 1.45 mmol), acetic acid (0.250 mL, 4.42 mmol), NaHB(OAc)₃ (770 mg, 3.63 mmol) and *tert*-butyl [(1*S*)-1-benzyl-2-oxoethyl]carbamate (620 mg, 2.49 mmol) in 5 mL of 1,2-dichloroethane was stirred overnight. The reaction mixture was partitioned between EtOAc and sat'd NaHCO₃, the organic layer was dried (Na₂SO₄), and concentrated. Chromatography on SiO₂ (EtOAc/hexanes, 1:19 to 1:1) gave 142 mg (22%) of the reductive amination product.

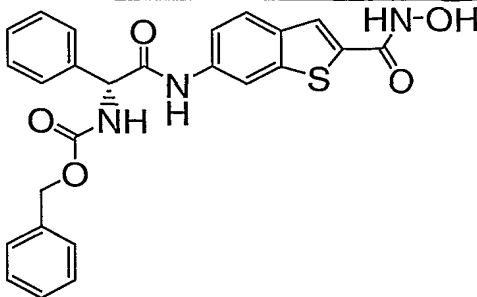
A portion of this methyl ester (40 mg, 0.091 mmol) was stirred for 2 days in 2 mL of 1:1 DMF/50% NH₂OH (aq). The reaction mixture was concentrated and purified by reverse-phase chromatography (10 to 100% MeCN/water with 0.05% TFA) giving 22 mg (53%) of the desired hydroxamic acid: ¹H NMR (600 MHz, DMSO-*d*₆) δ 11.14 (br s, 1 H), 10.42 (br s, 1 H), 7.77 (s, 1 H), 7.63 (br s, 1 H), 7.51 (d, *J* = 8.8 Hz, 1 H), 7.23-7.26 (m, 2 H), 7.15-7.18 (m, 3 H), 6.84 (d, *J* = 8.5 Hz, 1 H), 6.81 (s, 1 H), 6.73 (dd, *J* = 8.8, 1.8 Hz, 1 H), 3.78 (m, 1 H), 3.03-3.12 (m, 2 H), 2.79 (dd, *J* = 13.8, 5.6 Hz, 1 H), 2.66 (dd, *J* = 13.8, 8.8 Hz, 1 H), 1.28 (s, 9 H); MS: cal'd 442 (MH⁺), exp 442 (MH⁺).

Additional analogs were prepared in procedures similar to those described for the preparation of the above *tert*-butyl [(1*S*)-1-benzyl-2-({2-[(hydroxyamino)carbonyl]-1-benzothien-6-yl}amino)ethyl]carbamate.

The compounds described in the following tables were prepared by methods analogous to those synthetic methods described above, but using the appropriate starting reagents. The compounds listed in the tables below exhibit histone deacetylase inhibitory activity at concentrations of less than 0.5 μM.

Table 1

Cpd ID	Molecular Structure	Name
1		<i>tert</i> -butyl [(1 <i>S</i>)-1-benzyl-2-({2-[(hydroxyamino)carbonyl]-1-benzothien-6-yl}amino)ethyl]carbamate
2		<i>N</i> -hydroxy-6-[[[(4-methylphenyl)sulfonyl]amino}(phenyl)acetyl]amino]-1-benzothiophene-2-carboxamide
3		<i>N</i> -hydroxy-6-[[[(4-methoxyphenyl)sulfonyl]amino}(phenyl)acetyl]amino]-1-benzothiophene-2-carboxamide
4		<i>tert</i> -butyl [(1 <i>R</i>)-2-({2-[(hydroxyamino)carbonyl]-1-benzothien-6-yl}amino)-2-oxo-1-phenylethyl]carbamate
5		benzyl [(1 <i>S</i>)-2-({2-[(hydroxyamino)carbonyl]-1-benzothien-6-yl}amino)-2-oxo-1-phenylethyl]carbamate

6		benzyl [(1 <i>R</i>)-2-({2- [(hydroxyamino)carbonyl]-1- benzothien-6-yl}amino)-2-oxo-1- phenylethyl]carbamate
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EXAMPLE 2 – HDAC INHIBITION BY NOVEL COMPOUNDS

HDAC1-Flag Assay:

Novel compounds were tested for their ability to inhibit histone deacetylase, subtype 1 (HDAC1) using an in vitro deacetylation assay. The enzyme source for this assay was an epitope-tagged human HDAC1 complex immuno-purified from stably expressing mammalian cells. The substrate consisted of a commercial product containing an acetylated lysine side chain (BIOMOL Research Laboratories, Inc., Plymouth Meeting, PA). Upon deacetylation of the substrate by incubation with the purified HDAC1 complex, a fluorophore is produced that is directly proportional to the level of deacetylation. Using a substrate concentration at the K_m for the enzyme preparation, the deacetylation assay was performed in the presence of increasing concentrations of novel compounds to semi-quantitatively determine the concentration of compound required for 50% inhibition (IC_{50}) of the deacetylation reaction.

EXAMPLE 3 – HDAC INHIBITION IN CELL LINES

ATP Assay

The novel compounds of the present invention were tested for their ability to inhibit proliferation of the human cervical cancer (HeLa) and colon carcinoma (HCT116) cells.

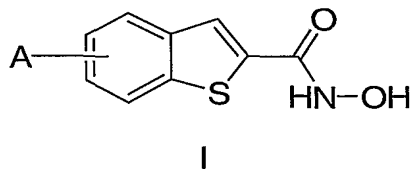
In this assay, also referred to as the Vialight Assay, cellular ATP levels are measured as a means of quantifying cellular proliferation. This assay makes use of a bioluminescent method from Cambrex (ViaLight PLUS, cat. #LT07-121). In the presence of ATP, luciferase converts luciferin to oxyluciferin and light. The amount of light produced (emission at 565nm) is measured and correlates with a relative amount of proliferation. Human cervical cancer (HeLa) or colon carcinoma (HCT116) cells were incubated with vehicle or increasing concentrations of compound for 48 hours. Cell proliferation was quantified by adding the cell lysis reagent (provided in the Vialight assay kit) directly to culture wells, followed by addition of the ATP-monitoring reagent (containing luciferase/luciferin). The amount of light produced is then measured (emission at 565nm). The quantity of light produced, as measured by 565nm absorbance, is directly proportional to the number of living cells in culture.

While this invention has been particularly shown and described with references to embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be

made therein without departing from the meaning of the invention described. Rather, the scope of the invention is defined by the claims that follow:

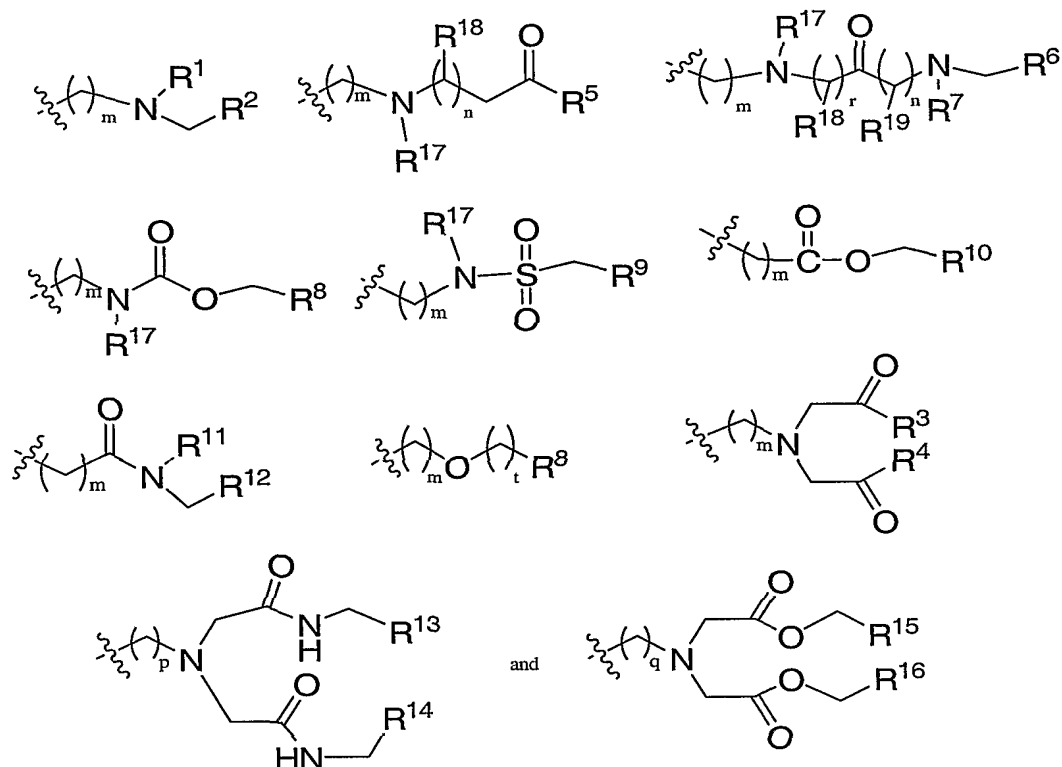
WHAT IS CLAIMED IS

1. A compound represented by the following structural Formula:



5

wherein A is a group selected from:



- 10 wherein R^2 to R^6 , R^8 to R^{10} and R^{12} to R^{16} are, independently of each other, a group selected from: substituted C_1 - C_{10} alkyl, substituted C_1 - C_{10} alkylaryl, substituted C_1 - C_{10} alkylcycloalkyl or substituted C_1 - C_{10} alkylheterocyclyl; wherein the alkyl portion of the group is substituted with a substituent that is independently selected from $-NR^{20}C(=O)R^{21}$, $-NR^{20}C(=O)OR^{21}$, $-C(=O)NR^{21}R^{22}$, $-NR^{20}SO_2R^{21}$ or $-NR^{20}C(=O)NR^{21}R^{22}$;

- 15 R^1 , R^7 , R^{11} and R^{17} to R^{20} are independently selected from hydrogen, unsubstituted or substituted C_1 - C_{10} alkyl, unsubstituted or substituted aryl, unsubstituted or substituted C_3 - C_8 cycloalkyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted C_1 - C_{10} alkylaryl, unsubstituted or substituted C_1 - C_{10} alkylcycloalkyl, or unsubstituted or substituted C_1 - C_{10} alkylheterocyclyl;

R^{21} is selected from unsubstituted or substituted C_1 - C_{10} alkyl, unsubstituted or substituted aryl, unsubstituted or substituted C_3 - C_8 cycloalkyl, unsubstituted or substituted heterocyclyl,

unsubstituted or substituted C₁-C₁₀ alkylaryl, unsubstituted or substituted C₁-C₁₀ alkylcycloalkyl, or unsubstituted or substituted C₁-C₁₀ alkylheterocyclyl;

R²² is selected from hydrogen, unsubstituted or substituted C₁-C₁₀ alkyl, unsubstituted or substituted aryl, unsubstituted or substituted C₃-C₈ cycloalkyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted C₁-C₁₀ alkylaryl, unsubstituted or substituted C₁-C₁₀ alkylcycloalkyl, or unsubstituted or substituted C₁-C₁₀ alkylheterocyclyl;

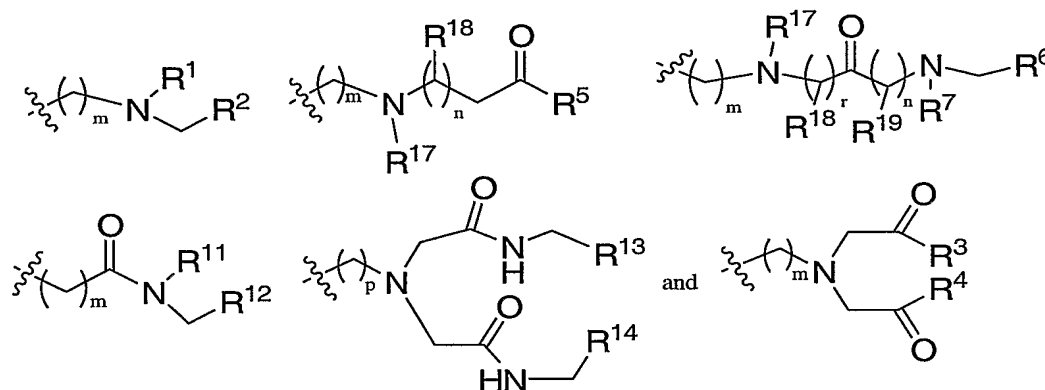
m, p and q are independently of each other 0, 1 or 2;

n and r are independently of each other 0, 1 or 2;

t is 1 or 2;

or a stereoisomer, enantiomer, racemate, pharmaceutically acceptable salt, solvate, hydrate or polymorph thereof.

2. The compound of claim 1, wherein A is selected from



and all of the other substituents are as described in claim 1.

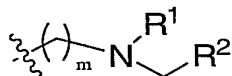
3. The compound of claim 2, wherein R¹⁸ and R¹⁹ are hydrogen.

4. The compound of claim 2, wherein r is 0 and n is 0.

5. The compound of claim 2, wherein R² to R⁶ and R¹² to R¹⁴ is independently selected from substituted -CH₂-phenyl, substituted -CH₂-naphthyl, substituted -CH₂-benzyl, substituted -CH₂-cyclohexyl, substituted -CH₂-quinolinyl, substituted -CH₂-isoquinolinyl, substituted -CH₂-pyridyl, -CH(Ph)₂, substituted -CH₂CH₂-phenyl, substituted -CH₂CH₂-naphthyl, substituted -CH₂CH₂-benzyl, substituted -CH₂CH₂-cyclohexyl, substituted -CH₂CH₂-quinolinyl, substituted -CH₂CH₂-isoquinolinyl, substituted -CH₂CH₂-pyridyl, substituted -CH₂CH(Ph)₂, substituted methyl, substituted ethyl, substituted propyl, substituted isopropyl, substituted butyl, substituted iso-butyl, substituted sec-butyl or substituted tert-butyl.

6. The compound of claim 2, wherein the alkyl portion of the R^2 to R^6 and R^{12} to R^{14} is substituted with a substituent that is independently selected from $-NR^{20}C(=O)OR^{21}$ or $-NR^{20}SO_2R^{21}$.

5 7. The compound of claim 1, wherein A is



R^1 and R^2 are as described in claim 1.

8. The compound of claim 7, wherein m is 0 or 1.

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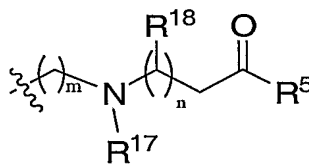
9. The compound of claim 7, wherein R^1 is hydrogen; and R^2 is substituted C_1 - C_{10} alkylaryl.

10. The compound of claim 9, wherein the alkyl portion of R^2 is substituted with a
15 substituent selected from $-NR^{20}C(=O)OR^{21}$ or $-NR^{20}SO_2R^{21}$.

11. The compound of claim 10, wherein R^{20} is hydrogen and R^{21} is unsubstituted or substituted C_1 - C_{10} alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted C_1 - C_{10} alkylaryl, or unsubstituted or substituted C_1 - C_{10} alkylheterocyclyl.

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12. The compound of claim 1, wherein A is



wherein R^5 is as described in claim 1, n is 0 and m is 0 or 1, and R^{17} is hydrogen.

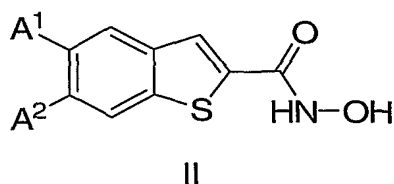
25 13. The compound of claim 12, wherein R^5 is substituted C_1 - C_{10} alkylaryl.

14. The compound of claim 13, wherein the alkyl portion of R^5 is substituted with a substituent selected from $-NR^{20}C(=O)OR^{21}$ or $-NR^{20}SO_2R^{21}$.

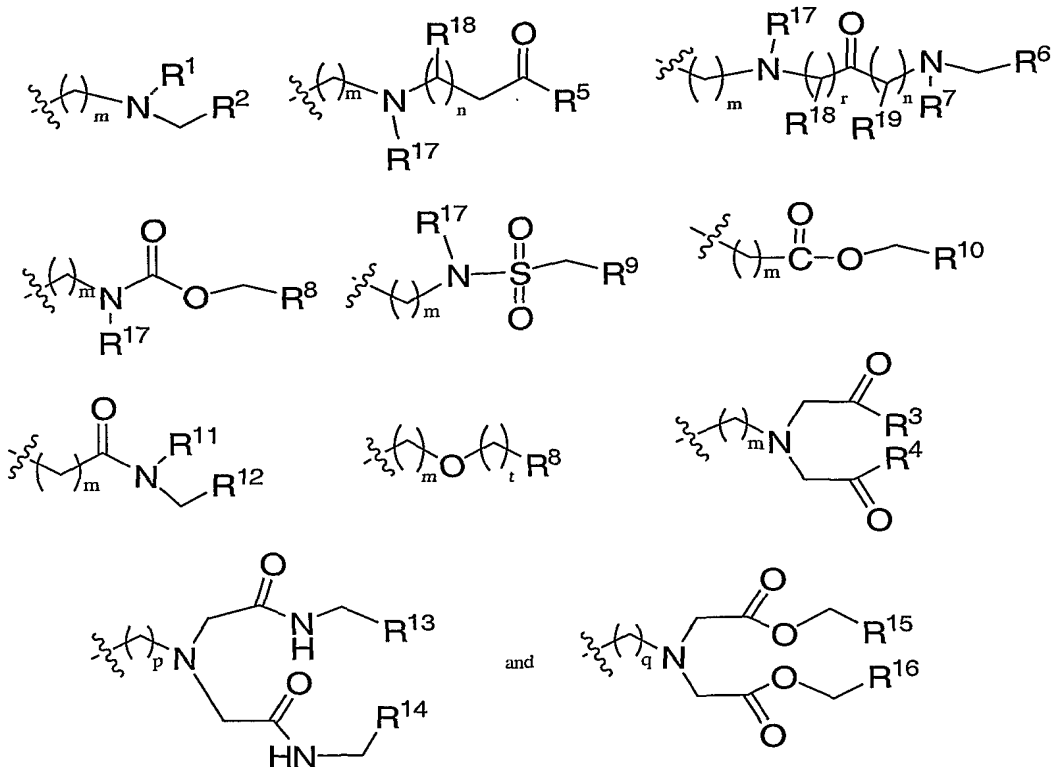
30 15. The compound of claim 14, wherein R^{20} is hydrogen and R^{21} is unsubstituted or

substituted C₁-C₁₀ alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted C₁-C₁₀ alkylaryl, or unsubstituted or substituted C₁-C₁₀ alkylheterocyclyl.

- 5 16. A compound represented by the following structural Formula:



wherein one of A¹ and A² is hydrogen and the other is a group selected from



- 10 wherein R² to R⁶, R⁸ to R¹⁰ and R¹² to R¹⁶ are, independently of each other, a group selected from: substituted C₁-C₁₀ alkyl, substituted C₁-C₁₀ alkylaryl, substituted C₁-C₁₀ alkylcycloalkyl or substituted C₁-C₁₀ alkylheterocyclyl; wherein the alkyl portion of the group is substituted with a substituent that is independently selected from -NR²⁰C(=O)R²¹, -NR²⁰C(=O)OR²¹, -C(=O)NR²¹R²², -NR²⁰SO₂R²¹ or -NR²⁰C(=O)NR²¹R²²;

- 15 R¹, R⁷, R¹¹ and R¹⁷ to R²⁰ are independently selected from hydrogen, unsubstituted or substituted C₁-C₁₀ alkyl, unsubstituted or substituted aryl, unsubstituted or substituted C₃-C₈ cycloalkyl,

unsubstituted or substituted heterocyclyl, unsubstituted or substituted C₁-C₁₀ alkylaryl, unsubstituted or substituted C₁-C₁₀ alkylcycloalkyl, or unsubstituted or substituted C₁-C₁₀ alkylheterocyclyl;

R²¹ is selected from unsubstituted or substituted C₁-C₁₀ alkyl, unsubstituted or substituted aryl, unsubstituted or substituted C₃-C₈ cycloalkyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted C₁-C₁₀ alkylaryl, unsubstituted or substituted C₁-C₁₀ alkylcycloalkyl, or unsubstituted or substituted C₁-C₁₀ alkylheterocyclyl;

R²² is selected from hydrogen, unsubstituted or substituted C₁-C₁₀ alkyl, unsubstituted or substituted aryl, unsubstituted or substituted C₃-C₈ cycloalkyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted C₁-C₁₀ alkylaryl, unsubstituted or substituted C₁-C₁₀ alkylcycloalkyl, or unsubstituted or substituted C₁-C₁₀ alkylheterocyclyl;

m, p and q are independently of each other 0, 1 or 2;

n and r are independently of each other 0, 1 or 2;

t is 1 or 2;

or a stereoisomer, enantiomer, racemate, pharmaceutically acceptable salt, solvate, hydrate or polymorph thereof.

17. A compound selected from:

tert-butyl [(1*S*)-1-benzyl-2-(2-[(hydroxyamino)carbonyl]-1-benzothien-6-yl)amino)ethyl]carbamate;

N-hydroxy-6-[[[(4-methylphenyl)sulfonyl]amino](phenyl)acetyl]amino-1-benzothiophene-2-carboxamide;

N-hydroxy-6-[[[(4-methoxyphenyl)sulfonyl]amino](phenyl)acetyl]amino-1-benzothiophene-2-carboxamide;

tert-butyl [(1*R*)-2-(2-[(hydroxyamino)carbonyl]-1-benzothien-6-yl)amino)-2-oxo-1-phenylethyl]carbamate;

benzyl [(1*S*)-2-(2-[(hydroxyamino)carbonyl]-1-benzothien-6-yl)amino)-2-oxo-1-phenylethyl]carbamate;

benzyl [(1*R*)-2-(2-[(hydroxyamino)carbonyl]-1-benzothien-6-yl)amino)-2-oxo-1-phenylethyl]carbamate;

or a stereoisomer, enantiomer, racemate, pharmaceutically acceptable salt, solvate, hydrate or polymorph thereof.

18. A method of inhibiting the activity of histone deacetylase 1 (HDAC-1), comprising contacting HDAC-1 with an effective amount of the compound of any one of claims 1-17 so as to inhibit the activity of HDAC-1.

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19. A method of treating cancer in a subject comprising administering to said subject a therapeutically effective amount of the compound of any one of claims 1-17.

20. A method of treating a thioredoxin (TRX)-mediated disease in a subject, comprising the step of administering to said subject a therapeutically effective amount of the compound of any one of claims 1-17, wherein the amount of said compound is effective to treat the TRX-mediated disease in said subject.

21. A method of treating a disease of the central nervous system in a subject comprising administering to said subject a therapeutically effective amount of the compound of any one of claims 1-17.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US06/14091

A. CLASSIFICATION OF SUBJECT MATTER

IPC: A61K 31/38(2006.01);C07D 333/22(2006.01)

USPC: 514/438;549/70,71

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/438; 549/70, 71

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ROMAGNOLI, R. Design, Synthesis, and Biological Evaluation of Hybrid Molecules contain methylene-butyrolactones and bromoacryloyl moieties, J. Med. Chem., 2005, Vol. 48, No. 24, pages 7906-7910, especially page 7906.	17
A	US 6,777,425 (BURLI et al) 17 August 2004 (17.08.2004), column 71, lines 50-70.	17
A	FR 2,825,706 (PIERRE FABRE MEDICAMENT) 06 June 2001 (06.06.2001), page 81, lines 1-40.	17

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

08 August 2006 (08.08.2006)

Date of mailing of the international search report

01 SEP 2006

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US06/14091

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1-16 and 18-21
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please See Continuation Sheet
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US06/14091

Continuation of Box II Reason 2:

The numerous variables, e.g., A, R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, etc... and their voluminous, complex meanings and their virtual incomprehensible permutations and combinations make it impossible to determine the full scope and complete meaning of the claimed subject matter. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT Article 6. Thus it is impossible to form a meaningful written opinion on these claims. A written opinion will be provided for the first discernable invention, which is Claim 17, tert-butyl[(1S)-1-benzyl-2-({2-[(hydroxyamino)carbonyl]-1-benzothien-6-yl}amino)ethyl]carbamate, limited to compounds containing the same core.